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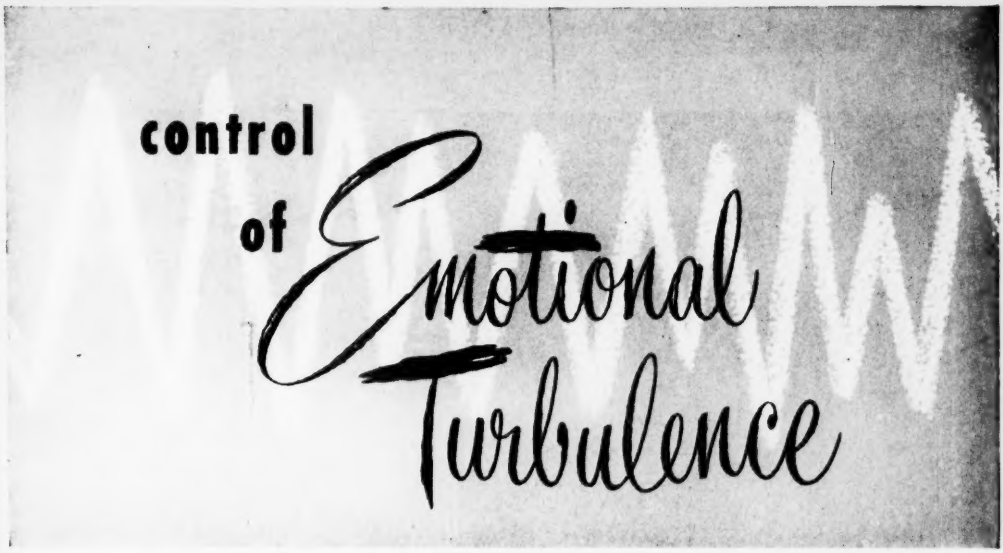

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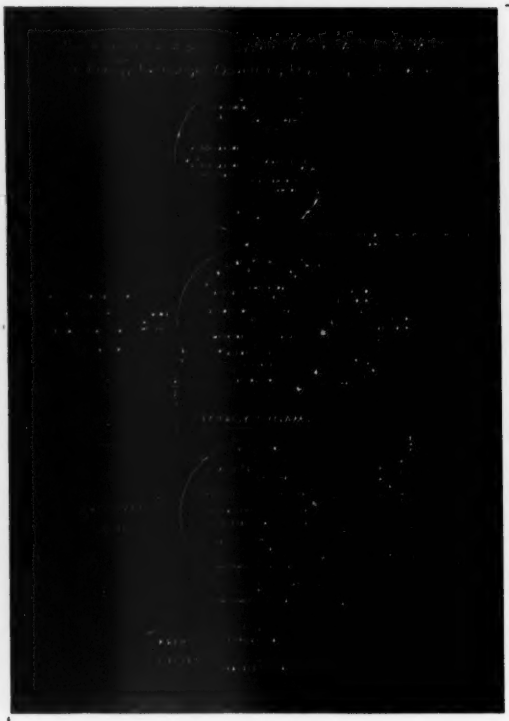

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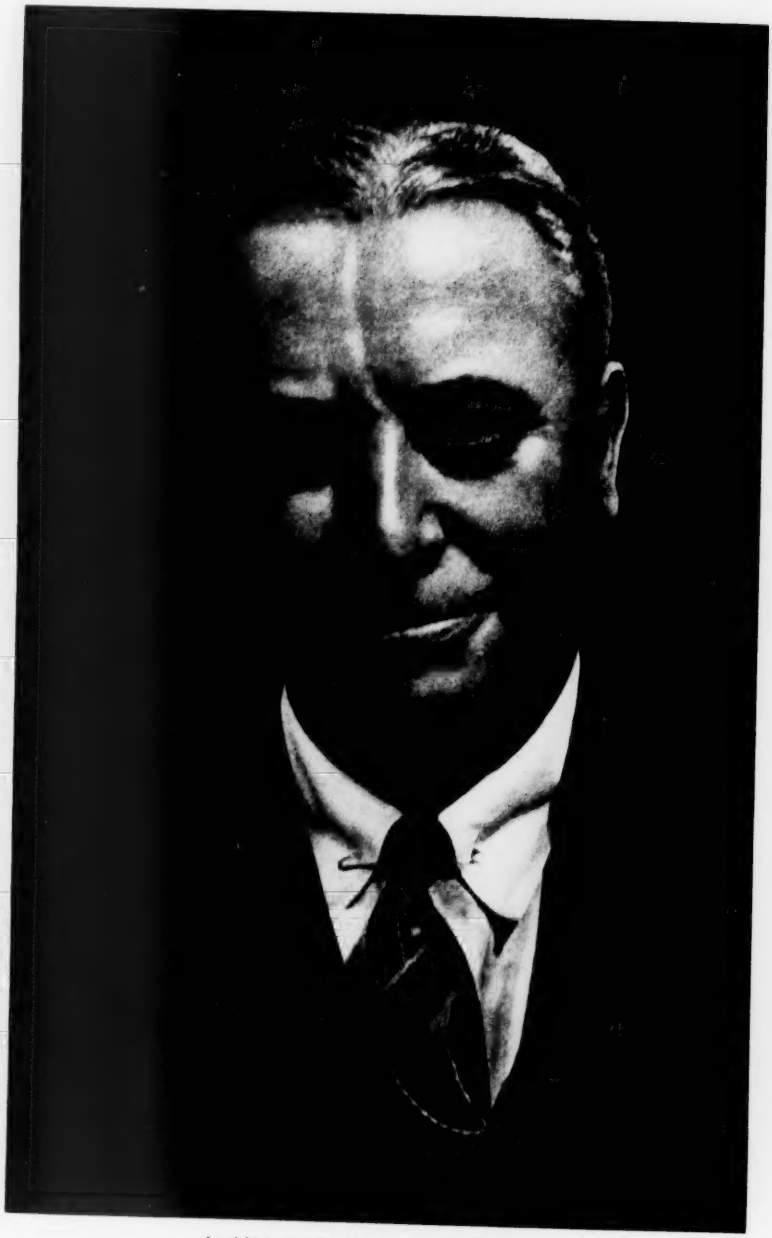

JOHN FARQUHAR FULTON

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THE LABORATORY OF PHYSIOLOGY

One of the first decisions—if not the very first—made by John Fulton when he came to Yale from his Magdalen Fellowship twenty five years ago was to name his new home the Laboratory of Physiology. I and others used to wonder why he made such a point of distinguishing between a Laboratory and a Department, but I believe that I now know. I believe that instinctively John chose the name to distinguish between environment for inquiry and a framework of organization. Certainly in the years that have passed there has been little enough of an organizational framework and none of the pyramidal academic structures seen with increasing frequency these days. Rather there was provided an environment that yielded a maximum of stimulation and a minimum of direction, and much perspective, and little direct assistance. In short, it was an environment aimed primarily at the development of individuals and their personal philosophy of Physiology, rather than the physiology of the Professor.

Many and varied have been the studies undertaken in the Laboratory in consequence of this orientation: neurophysiology, electrocardiology, endocrinology, aviation physiology. All, as they are reviewed in the annual volumes of publications from the Laboratory, bear some imprint of John Fulton's influence, perhaps directly in initiation, more often in careful formulation of a problem, usually in some aspect of technique, almost always in the discussion of the relation of the study to other work, and invariably in advice toward direct, expressive writing and that nice appreciation and recognition of the work of others which comes from historical perspective.

Even more varied have been the students attracted to the Laboratory by the challenge to their individual abilities: neurosurgeons, neurologists, graduate students, historians, and physiologists of all specialties. Few have been of the kind to make docile assistants, or long suffering academic wheel horses, even in John's own domain, and no department of physiology anywhere has developed professors in such a wide spectrum of academic endeavor: in Physiology, Neurosurgery, Neurology, and in Medical Administration.

What have been the other features of the Laboratory that have made it so unique an expression of J.F.F.'s own philosophy, and such a real influence

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in medical education today? First of all I would list its humanistic approach. John perhaps should have been a surgeon, so that he could savor some of the satisfaction that comes from direct intervention for the benefit of a patient, but I suspect he has enough of the humanistic philosophy of the great iatrophilosophers like Rabelais to have garnered the less heady satisfaction of indirect assuagement of human needs. Like the father of daughters, his contributions will be found even where his name may not be known. Certainly the Laboratory understood the difference between immediate and long-range practicality and felt secure enough in its competence in both practical matters and "pure" science to make a fetish of neither.

From this humanistic approach no doubt derived the clinical approach to physiology that so strongly characterized the Laboratory. Charcot's exclamation, "Ce n'est pas un singe, c'est un malade!" might well have been a Laboratory motto. Careful observation of behavior, close examination by the unaided senses, and a minimum of instrumentation were emphasized as the necessary fundamentals of all good research. To these J.F.F. himself contributed a peerless neurosurgical technique and encouraged the development of advanced instrumentation in psychobiology and electrophysiology as it became imperative, but the orientation in the Laboratory has always been toward the problem and never toward the means themselves.

From the beginning, the clinical approach extended to and merged with the behavioral. The doctrine of cortical localization, so firmly based upon the plan of topographical projection in the nervous system and so presciently extrapolated to the autonomic nervous system in almost the first studies from the new Laboratory, was early seized upon as a key to behavior. Today this work stands at the very threshold of the newest era in neurophysiology, when the vagaries of human behavior can be expressed in neurophysiological terms and all the links in the chain from neurone to mind will be recognized.

The Laboratory was created as part of a new plan in medical education at Yale, and one day there will have to be an evaluation of this plan and of the very large part that the Laboratory of Physiology played in upholding its principles. To me the very essence of the Yale Plan was that it placed its main emphasis on learning rather than teaching. Fortunately, therefore, the Laboratory atmosphere was thus the same for medical student, graduate student, fellow, and faculty in its emphasis on personal initiative and its provision for an environment in which learning took place. As a result, the schizophrenia that so often grows up between teaching and research duties was noticeably absent. It is by no means paradoxical that such an atmosphere should develop strong attitudes about teaching and cultivate so many

good teachers. The Laboratory of Physiology was thus almost uniquely fortunate in the direct and indirect support it received from the School of Medicine and the University.

I suspect that the most significant characteristic of the Laboratory was the catholicity or universality of its outlook. No small part of this came from the historical perspective that oriented the day's work against the labors of the past. Books were the vehicle of history, and they lay open in the laboratory as well as in the seminar room and library. No one knew better than J.F.F. where to turn for the apposite passage in them. His affection for them is our reason for compiling one on this occasion and presenting it now to him.

Twenty-five years are swiftly past but they have encompassed a period of real significance for all of us who have been associated with the Laboratory of Physiology and its creative genius whom we salute today.

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BIBLIOGRAPHY OF JOHN FARQUHAR FULTON

1920

1. The blood of Ascidia atra Lesueur, with special reference to pigmentation and phagocytosis. Acta zool. Stockh., 1920, *1*, 381–431.

1921

2. The controlling factors in amphibian metamorphosis. Endocrinology, 1921, *5*, 67–84.
3. Novocaine as a substitute for curare. Proc. nat. Acad., Wash., 1921, *7*, 114.
4. The catalytic properties of the respiratory metals. Science, 1921, *53*, 444–446.
5. Concerning the vitality of Actinia bermudensis: a study in symbiosis. J. exp. Zool., 1921, *33*, 353–364.
6. Studies on neuromuscular transmission. I. The action of novocaine on muscle nuclei. Amer. J. Physiol., 1921, *57*, 153–170.

1922

7. Animal chlorophyll. Its relation to haemoglobin and to other animal pigments. Quart. J. micr. Sci., 1922, *66*, 339–396.

1923

8. Trichodina pediculus and a newly related species. Proc. Boston Soc. nat. Hist., 1923, *37*, 1–29.

1924

9. The influence of temperature on the action of insulin. Nature, 1924, *113*, 234–235 (with J. Huxley[1]).
10. Lapicque's investigations on the chronaxie of excitable tissues. Nature, 1924, *113*, 429–430.
11. "After-discharge" in a peripheral nerve muscle preparation as influenced by the state of the circulation and the initial passive stretch. J. Physiol., 1924, *58*, xxxvi–xxxvii.
12. The thresholds of functionally different fibres in a mixed nerve (uncut). J. Physiol., 1924, *59*, vii–viii.
13. The influence of initial tension upon the magnitude and duration of the mechanical response in skeletal muscle. Proc. roy. Soc., 1924, *96B*, 475–490.
14. Observations on the latent period of skeletal muscle. J. Physiol., 1924, *59*, xlvii–xlviii.

1925

15. The influence of tension upon the electrical responses of muscle to repetitive stimuli. Proc. roy. Soc., 1925, *97B*, 406–423.
16. Some observations upon the electrical responses and shape of the isometric twitch of skeletal muscle (intact). Proc. roy. Soc., 1925, *97B*, 424–431.
17. The relation between the durations of the isometric twitch and of the after-action of tetanus. Proc. roy. Soc., 1925, *97B*, 431–443.
18. The temperature coefficient of muscle viscosity. J. Physiol., 1925, *60*, xix–xx.
19. A correlation of the size of the action current of skeletal muscle with length, tension and initial heat production. J. Physiol., 1925, *60*, xxi–xxii.
20. Fatigue and plurisegmental innervation of individual muscle fibres. Proc. roy. Soc., 1925, *98B*, 493–505.
21. The latent period of skeletal muscle. Quart. J. exp. Physiol., 1925, *15*, 349–366.
22. Observations on ipsilateral contraction and "inhibitory" rhythm. Proc. roy. Soc., 1925, *98B*, 214–227 (with E. G. T. Liddell).
23. Electrical responses of extensor muscle during postural (myotatic) contraction. Proc. roy. Soc., 1925, *98B*, 577–589 (with E. G. T. Liddell).

24. Observations on spinal and decerebrate knee jerks with special reference to their inhibition by single break shocks. Proc. roy. Soc., 1925, *98B*, 589-607. (with L. Balliff [1] and E. G. T. Liddell).

25. On the summation of contractions in skeletal muscle. Amer. J. Physiol., 1925, *75*, 211-234.

26. The influence of shortening on the size of the action current and the duration of the mechanical response in skeletal muscle. Amer. J. Physiol., 1925, *75*, 235-260.

27. The inseparability of mechanical and electrical responses in skeletal muscle. Amer. J. Physiol., 1925, *75*, 261-266.

1926

28. John Newport Langley (1852-1925). M.A., M.D., LL.D., F.R.S. J. nerv. ment. Dis., 1926, *63*, 98-101.

29. Reciprocal innervation of antagonistic muscles and the coordination of movement. Arch. Neurol. Psychiat., Chicago, 1926, *16*, 650-652.

30. The mechanism of the postural contraction (tonus) of skeletal muscle. Proc. Soc. exp. Biol., N. Y., 1926, *23*, 700-703.

31. *Muscular contraction and the reflex control of movement. A monograph.* Baltimore, Williams and Wilkins Co., 1926. xv, 644 pp.

1927

32. The early phrenological societies and their journals. Boston med. surg. J., 1927, *196*, 398-403, 427-432.

33. Ernest Henry Starling, M.D., B.S., F.R.S., F.R.C.P. (1866-1927). Boston med. surg. J., 1927, *196*, 888-889.

34. The nature of the material in liver effective in pernicious anaemia. I. J. biol. Chem., 1927, *74*, 69-72. (with E. J. Cohn [1], G. R. Minot, H. F. Ulrichs, F. C. Sargent, J. H. Weare, and W. P. Murphy).

35. Observations upon the knee jerk in "high" and "low" spinal preparations. Amer. J. Physiol., 1927, *81*, 487. (with P. M. Harmon [1]).

36. Observations upon temporal summation and upon inhibition of the crossed extensor reflex before and after deafferentation. Amer. J. Physiol., 1927, *81*, 503-550. (with J. Pi Suñer [1]).

37. The relative duration of contraction in flexors and in extensors. Amer. J. Physiol., 1927, *81*, 462-463. (with P. C. Baird, Jr. [1]).

38. Rudolph Magnus (1872-1927). Boston med. surg. J., 1927, *196*, 323-324.

39. William Einthoven (1860-1927). Dr. Med. Boston med. surg. J., 1927, *196*, 687-688.

40. The effect of reflex excitation and inhibition on the response of a muscle to stimulation through its motor nerve. Amer. J. Physiol., 1927, *82*, 693-716. (with A. Forbes [1] and L. R. Whitaker).

1928

41. The influence of the proprioceptive nerves of the hind limbs upon the posture of the fore limbs in decerebrate cats. Amer. J. Physiol., 1928, *83*, 548-553. (with J. Pi Suñer [1]).

42. A note concerning the probable function of various afferent end-organs in skeletal muscle. Amer. J. Physiol., 1928, *83*, 554-562. (with J. Pi Suñer).

43. El reflejo rotuliano. Rev. méd. Barcelona, 1927. (Dec., 11 pp.).

44. The influence of the proprioceptive system upon the crossed extensor reflex. Amer. J. Physiol., 1928, *88*, 453-467. (with J. Pi Suñer [1]).

45. Some clinical observations upon the physiology of the hypothalamus. Amer. J. Physiol., 1928, *85*, 372. (with P. Bailey).

46. Contribution to the study of tumors in the region of the third ventricle: their diagnosis and relation to pathological sleep. J. nerv. ment. Dis., 1929, *69*, 1-25; 145-164; 261-277 (with P. Bailey).
47. A clinical and pathological study of two teratomatous cysts of the spinal cord, containing mucus and ciliated cells. Surg. Gynec. Obstet., 1928, *47*, 297-311 (with L. S. Kubie [1]).
48. Vasomotor and reflex sequelae of unilateral, cervical and lumbar ramisectomy in a case of Raynaud's disease, with observations on tonus. Ann. Surg., 1928, *81*, 827-841.
49. Observations upon the vascularity of the human occipital lobe during visual activity. Brain, 1928, *51*, 310-320.

1929

50. Horner and the syndrome of paralysis of the cervical sympathetic. Arch. Surg., Chicago, 1929, *18*, 2025-2039.
51. The early history of percussion. Brit. med. J., 1929, *1*, 708.
52. Robert W. Smith's description of generalized neurofibromatosis (1849). New Engl. J. Med., 1929, *200*, 1315-1317.
53. Emotional disturbances following experimental lesions of the base of the brain (pre-chiasmal). J. Physiol., 1929, *67*, xxvii-xxviii; Amer. J. Physiol., 1929, *90*, 353 (with F. D. Ingraham).
54. Letter to the Editor of *The Times* [re. Sir Humphry Davy], 14 June 1929.
55. James Black's description of contractility of capillaries (1824). Lancet, 1929, *2*, 1010.
56. The 13th International Physiological Congress. Bull. Harvard Med. Sch. Alumni Ass., 1929, *1*, 4-8.
57. Edward Selleck Hare (1812-1838) and the syndrome of paralysis of the cervical sympathetic. Proc. R. Soc. Med. (Hist. Sec.), 1929, *23*, 152-157.
58. A case of cerebellar tumor with seizures of head retraction described by Wurfbain in 1691. J. nerv. ment. Dis., 1929, *70*, 577-583.

1930

59. Nueva contribución sobre los tumores del tercer ventrículo. Su asociación con el sindrome de Recklinghausen y con el edema de Quincke. Arch. argent. Neurol., 1930, *5*, 3-27 (with P. Bailey).
60. Nervous integrations in man. Chapt. XI in: Cowdry, *Human biology and racial welfare*. New York, Paul B. Hoeber, 1930 (with C. S. Sherrington).
61. Experimental observations on the action of Radon on the spinal cord. Lancet, 1930, *2*, 16 (with H. Cairns [1]).
62. The influence of experimental lesions of the spinal cord upon the knee-jerk. I. Acute lesions. Brain, 1930, *53*, 311-326 (with E. G. T. Liddell and D. Rioch). (Preliminary note: The influence of experimental lesions of the spinal cord upon the knee-jerk and crossed extensor reflexes. J. Physiol., 1930, *69*, xxvii-xxviii).
63. The influence of unilateral destruction of the vestibular nuclei upon posture and the knee-jerk. Brain, 1930, *53*, 327-343 (with E. G. T. Liddell and D. Rioch). (Preliminary note: J. Physiol., 1930, *70*, xxiii).
64. "Dial" as a surgical anaesthetic for neurosurgical operations; with observations on the nature of its action. J. Pharmacol., 1930, *40*, 423-432 (with E. G. T. Liddell and D. Rioch). (Preliminary note: Dial as an anaesthetic for surgical operations on the nervous system. J. Physiol., 1930, *70*, xxiii).
65. The physiological basis of the surgery of the sympathetic nervous system. New Engl. J. Med., 1930, *203*, 555-561.
66. *Selected readings in the history of physiology*. Springfield, Ill., Charles C Thomas, 1930. xx, 317 pp.
67. A note on the origin of the term "physiology." Yale J. Biol. Med., 1930, *3*, 59-62.

1931

68. *Physiology. Clio medica series of primers of the history of medicine.* New York, Paul B. Hoeber, 1931. xvi, 146 pp.

69. The rise of the experimental method: Bacon and the Royal Society of London. Yale J. Biol. Med., 1931, *3*, 299-320.

70. The functional activity of single units in the central nervous system. Science, 1931, *73*, 685-692.

71. The effect of emotional stress on blood fat. Amer. J. Physiol., 1931, *97*, 533 (with H. E. Himwich [1]).

72. The action of anesthetic drugs on the motor cortex of monkeys. Amer. J. Physiol., 1931, *97*, 537.

73. Early medical humanists: Leonicenus, Linacre and Thomas Elyot. New Engl. J. Med., 1931, *205*, 141-146.

74. The genesis of cerebellar tremor and its disappearance after removal of the cerebral hemispheres. Science, 1931, *74*, 578.

1932

75. A bibliography of the Honorable Robert Boyle. Proc. Oxford bibliogr. Soc., 1932, *3*, 1-160.

76. Exhibit illustrating the history of science. Yale Univ. Libr. Gaz., 1932, *6*, 59-64.

77. Haller and the humanization of bibliography. Annual Oration of the Boston Medical Library. New Engl. J. Med., 1932, *206*, 323-328.

78. Observations on the response of the same chimpanzee to dial, amytal and nembutal, used as surgical anaesthetics. Surg. Gynec. Obstet., 1932, *54*, 764-770 (with A. D. Keller).

79. Claude Bernard and the future of medicine. Canad. med. Ass. J., 1932, *27*, 427-433.

80. *The sign of Babinski. A study of the evolution of cortical dominance in primates.* Springfield, Ill., Charles C. Thomas, 1932. xv, 165 pp. (with A. D. Keller).

81. Bilateral representation of the lower extremity in the motor cortex of the chimpanzee. Amer. J. Physiol., 1932, *101*, 36.

82. Yale University School of Medicine, Department of Physiology. Pp. 17-23 in: *Methods and problems of medical education*, 20th series. New York, The Rockefeller Foundation, 1932.

83. State of the flexor reflex in paraplegic dog and monkey respectively. J. Physiol., 1932, *75*, 17-22 (with C. S. Sherrington).

84. Robert Boyle and his influence on thought in the seventeenth century. Isis, 1932, *18*, 77-102.

85. New horizons in physiology and medicine; the hypothalamus and visceral mechanisms. New Engl. J. Med., 1932, *207*, 60-68.

86. Relation of the cerebrum to the cerebellum. I. Cerebellar tremor in the cat and its absence after removal of the cerebral hemispheres. Arch. Neurol. Psychiat., Chicago, 1932, *28*, 542-567 (with E. G. T. Liddell and D. McK. Rioch).

87. The influence of unilateral and bilateral extirpation of the cortical representation of the upper extremities on acquired skilled movements in primates. X. Int. Congr. exp. Psychol., 1932 [1 p.] (with C. F. Jacobsen [1]).

88. The motor cortex of the black bear and the results of extirpating the motor representation of the hind foot. XIV. Int. physiol. Congr. (Sunto), 1932, 78. Arch. Sci. biol., Napoli, 1933, *18*, 132-133 (with J. H. Ferguson [1]).

89. An experimental analysis of the evolution of cortical dominance in primates. XIV. Int. physiol. Congr. (Sunto), 1932, 88. Arch. Sci. biol., Napoli, 1933, *18*, 141-142.

90. A study of cortical representation of the lower extremities in the gibbon. XIV. Int. physiol. Congr. (Sunto), 1932, 133. Arch. Sci. biol., Napoli, 1933, *18*, 196-197 (with Margaret V. Kennard [1]).

91. The relation of the pyramidal tract to spinal "shock." XIV Int. physiol. Congr. (Sunto), 1932, 175. Arch. Sci. biol., Napoli, 1933, *18*, 247-248. (with G. P. McCouch [1].)

92. The Nobel prize in physiology and medicine for 1932. Science, 1932, *76*, 427-429.

93. The Nobel prize in physiology and medicine: Sir Charles Sherrington. Scientific Monthly, 1932, *35*, 568-569.

94. A note concerning the relation of the frontal lobes to posture and forced grasping in monkeys. Brain, 1932, *55*, 524-536. (with C. F. Jacobsen and Margaret A. Kennard.)

1933

95. Joseph François Félix Babinski. Arch. Neurol. Psychiat., Chicago, 1933, *29*, 168-174. Reprinted: J. nerv. ment. Dis., 1933, *77*, 111-118.

96. Science in the clinic as exemplified by the life and work of Joseph Babinski. J. nerv. ment. Dis., 1933, *77*, 121-133.

97. The Warrington Academy (1757-1786) and its influence upon medicine and science. Suppl. Bull. Johns Hopk. Hosp., 1933, *52*, 50-80. (Bull. Hist. Med., 1933, *1*, 50-80).

98. The representation of the tail in the motor cortex of primates, with special reference to spider monkeys. J. cell. comp. Physiol., 1933, *2*, 399-426. (with J. G. Dusser de Barenne.)

99. The relation of forced grasping and groping to the righting reflexes. Amer. J. Physiol., 1933, *105*, 7-8. (with I. Bieber [1].)

100. The localizing significance of spasticity, reflex grasping, and the signs of Babinski and Rossolimo. Brain, 1933, *56*, 213-225. (with Margaret A. Kennard [1].) (Preliminary note: The relation of the motor and premotor areas of the cortex to spasticity and postural reflexes in primates. Amer. J. Physiol., 1933, *105*, 35.)

101. Medicine. Science, 1933, *78*, 109-114.

102. *Handlist of editions of the poem* Syphilis sive morbus Gallicus *by Girolamo Fracastoro of Verona.* Oxford, Privately printed at the University Press, 1933. viii, 19 pp. (with Leona Baumgartner [1].)

103. William Beaumont's letter to his New Haven bookseller, Hezekiah Howe, with a bibliographical description of the editions of Beaumont's book. Yale J. Biol. Med., 1933, *6*, 9-17. (with Charlotte H. Peters [1].)

104. Ipsilateral representation in the motor and premotor cortex of monkeys. Brain, 1933, *56*, 318-342. (with P. C. Bucy [1].)

105. The bicentenary exhibition of Joseph Priestley. Yale Univ. Libr. Gaz., 1933, *8*, 63-73. (with Winnifred Reid [1].)

106. Addenda to a bibliography of the Honourable Robert Boyle. Proc. Oxford bibliogr. Soc., 1933, *3*, 339-365.

1934

107. Forced grasping and groping in relation to the syndrome of the premotor area. A physiological analysis. Arch. Neurol. Psychiat., Chicago, 1934, *31*, 221-235.

108. Bibliographical note concerning the first edition of *De venarum ostiolis*, pp. 31-36 in: *De venarum ostiolis, 1603, of Hieronymus Fabricius of Aquapendente (1533-1619)*, facsimile and translation by K. J. Franklin. Springfield, Ill., Charles C. Thomas, 1934.

109. A study of flaccid and spastic paralyses produced by lesions of the cerebral cortex. Res. Publ. Ass. nerv. ment. Dis., 1934, *13*, 158-210. (with Margaret A. Kennard.)

110. Intussusception: the relation of the cerebral cortex to intestinal motility in the monkey. New Engl. J. Med., 1934, *210*, 883-896. (with J. W. Watts [1].)

111. Some function of the cerebral cortex. I. Autonomic representation in the cerebral cortex. II. The frontal lobes. Beaumont Foundation Lectures. J. Mich. med. Soc., 1934, *33*, 175-182; 235-243.

112. The syndrome of the premotor cortex in man. Impairment of skilled movements, forced grasping, spasticity, and vasomotor disturbance. Brain, 1934, *57*, 69-84 (with Margaret A. Kennard [1] and H. R. Viets)

113. The principles of bibliographical citation: an informal discourse addressed to writers of scientific papers. Bull. med. Libr. Ass., 1934, *22 n.s.*, 183-197. Tr. into Spanish by Felipe Mendoza: Las normas fundamentales de las citas bibliograficas) in Prensa med. Mexicana, 1946, *11*, 95-99. Tr. into Portuguese by S. T. Napoli in Rev. bibliographica "Torres," 1954, *6*, 15 pp.

114. Autonomic representation in the cerebral cortex. Amer. J. Physiol., 1934, *109*, 37 (with Margaret A. Kennard and J. W. Watts)

115. Charles Darwin (1758-1778) and the history of the early use of digitalis. Bull. N. Y. Acad. Med., 1934, *10*, 496-506

116. The nomenclature of primates commonly used in laboratory work. New Haven, Privately printed, 1934. 14 pp. (with S. Zuckerman [1])

117. Benjamin Gale, pp. 185-187 in: Perry, C. E., ed., *Founders and leaders of Connecticut, 1633-1783*. Boston, D. C. Heath and Co. [1934]

118. The menstrual cycle of the primates. VII. The sexual skin of the chimpanzee. J. Anat., Lond., 1934, *69*, 38-46 (with S. Zuckerman [1])

119. Paralyses of cortical origin. A physiological analysis of flaccid and spastic states in monkeys and chimpanzees. Proc. Calif. Acad. Med., 1934, *1*, 1-20

1935

120. The effect of lesions of the hypothalamus upon the gastro-intestinal tract and heart in monkeys. Ann. Surg., 1935, *101*, 363-372 (with J. W. Watts [1])

121. Upper motor neuron lesions. An analysis of the syndromes of the motor and the premotor areas. J. Amer. med. Ass., 1935, *104*, 357-362 (with H. R. Viets). (Reprinted: Physiother. Rev., 1935, *15*, 107-109.)

122. The uncrossed lateral pyramidal tract in higher primates. J. Anat., Lond., 1935, *69*, 181-187 (with D. Sheehan).

123. *A bibliography of the poem* Syphilis sive morbus gallicus *by Girolamo Fracastoro of Verona*. New Haven, Yale University Press, 1935. 158 pp. (with Leona Baumgartner [1])

124. *Seiri-gaku shisu*. [Selected readings in the history of physiology, tr. by Susumu Harashima] Tokyo, Iwanami, 1933. 406 pp.

125. A note on the definition of the "motor" and "premotor" areas. Brain, 1935, *58*, 311-316

126. A bibliography of two Oxford physiologists: Richard Lower, 1631-1691 and John Mayow, 1643-1679. Proc. Oxford bibliogr. Soc., 1935, *1*, 1-62

127. The functions of the frontal lobes: a comparative study in monkeys, chimpanzees and man. Advances mod. Biol., 1935, *1*, 113-122 (with C. F. Jacobsen)

128. The significance of overlapping somatic and autonomic representation in the premotor area (area 6a). Sechenov J. Physiol. USSR, 1935, *21*, 39

1936

129. Somatic and autonomic motor functions of the cerebral cortex in ape and man. XII. Ludvig Hektoen Lecture on the Frank Billings Foundation. Proc. Inst. Med., Chicago, 1936, *11*, 21-42

130. Ivan Petrovitch Pavlov. New Engl. J. Med., 1936, *214*, 487-489

131. Ivan Petrovitch Pavlov. Scientific Monthly, 1936, *42*, 374-377

132. Relation of the cerebrum to the cerebellum. II. Cerebellar tremor in the monkey and its absence after removal of the principal excitable areas of the cerebral cortex (areas 4 and 6a, upper part). III. Accentuation of cerebellar tremor following lesions of the premotor area (area 6a, upper part). Arch. Neurol. Psychiat., Chicago, 1936, *35*, 439-466 (with C. D. Aring [1])

133. The effects of occipital lobectomy on vision in chimpanzee. Brain, 1936, *59*, 35-60.

134. John Scott Haldane. New Engl. J. Med., 1936, *214*, 651-652.

135. Somatic sensory function of the cerebral cortex in the monkey and chimpanzee. Amer. J. Physiol., 1936, *116*, 134-135. (with T. C. Ruch [11]).

136. A bibliographical study of the Galvani and the Aldini writings on animal electricity. Ann. Sci., 1936, *1*, 239-268. (with Harvey Cushing.)

137. El naixement del metode experimental. Vol. I, pp. 11-50 in: Bernard, C. *Introduccio a l'estudi de la medicina experimental*, tr. by J. Pi Suñyer. Bayo, Barcelona, Arnau de Vilanova, 1936. 2 v. (Translation of No. 68.)

138. The interrelation of cerebrum and cerebellum in the regulation of somatic and autonomic functions. Medicine, 1936, *15*, 247-306.

139. Edward Wotton (1492-1555). Zoologist, physician, Fellow of Magdalen College, Oxford. Verh. schweiz. Naturforsch. Ges., 1936. [1 p.]

140. The Nobel Prize in medicine 1936. Dale and Loewi and the previous Nobel Prize men in physiology and medicine. New Engl. J. Med., 1936, *215*, 989-990; 992-994.

141. The external configuration of the cerebral hemispheres of the chimpanzee. J. Anat., Lond., 1936, *71*, 105-116. (with A. E. Walker [11]).

142. Cerebral regulation of autonomic function. Proc. interstate post-grad. med. Assembly, No. Amer., 1936, 149-154.

1937

143. Further experiments on the somato-sensory functions of the cerebral cortex in the monkey and chimpanzee. Amer. J. Physiol., 1937, *119*, 394-395. (with T. C. Ruch [11] and S. Kasdon).

144. The relation of the motor area of primates to hyporeflexia ("spinal shock") of spinal transection. J. nerv. ment. Dis., 1937, *86*, 125-146. (with G. P. McCouch).

145. Works of Joseph Priestley, 1733-1804. Preliminary short title list. Privately printed. 20 pp. (with Charlotte H. Peters).

146. The centenary of the first American Physiological Society founded at Boston by William A. Alcott and Sylvester Graham. Bull. Hist. Med., 1937, *5*, 687-734. (with H. E. Hoff [11]).

147. The cerebellum. A summary of functional localization. Yale J. Biol. Med., 1937, *10*, 89-119. (with R. S. Dow).

148. Humanism in bibliography. Special Libraries, 1937, *28*, 279-283.

149. A memorandum on Journal of Neurophysiology. New Haven, 1937. 4 pp. (with J. G. Dusser de Barenne [11] and R. W. Gerard).

150. *Sir Kenelm Digby, Horter, bibliophile and protagonist of William Harvey*. New York, Peter and Katharine Oliver, 1937. 75 pp.

151. A note on Francesco Gennari and the early history of cytoarchitectural studies of the cerebral cortex. Bull. Hist. Med., 1937, *5*, 895-913.

152. Spasticity and the frontal lobes. New Engl. J. Med., 1937, *217*, 1017-1024. Also translation by F. K. Kessel. Spastizität und Stirnlappen. Nervenarzt, 1938, *11*, 448-457.

1938

153. The early history of the lymphatics. With particular reference to Bartholin, Rudbeck and Jolyffe. Bull. Hennepin Co. med. Soc., 1938, *9*, 5-10.

154. An English translation of Sandstrom's *Glandulae parathyreoideae*, by Carl M. Seipel, with biographical notes by J. August Hammar, edited by Charlotte H. Peters and J. F. Fulton. Bull. Hist. Med., 1938, *6*, 179-222.

155. Relation of the cerebral cortex to the grasp reflex and to postural and righting reflexes. Arch. Neurol. Psychiat., Chicago, 1938, *39*, 433-454. (with J. Bieber [11]).

156. Functional recovery in ocular muscles of a chimpanzee after section of oculomotor nerve. J. Neurophysiol., 1938, *1*, 144-151. (with M. B. Bender [11]).

157 An introduction to a bibliography of the educational and scientific works of Joseph Priestley. Pap bibliogr. Soc. Amer., 1936, *30*, 150-167 [issued May 1938] (with Charlotte H. Peters).

158 Hemidecortication in chimpanzee, baboon, macaque, potto, cat and coati. J. nerv. ment. Dis., 1938, *87*, 677-700 (with A. E. Walker [1]).

159 Sensory discrimination in monkey, chimpanzee and man after lesions of the parietal lobe. Arch. Neurol. Psychiat., Chicago, 1938, *39*, 919-938 (with J. C. Rich [1] and W. J. Germann).

160 *Physiology of the nervous system*. New York, Oxford University Press, 1938, xxi, 675 pp.

161 Pancreatectomy in the monkey. Amer. J. Physiol., 1938, *123*, 33 (with Sarah W. Chapman [1]).

162 Functional localization in the cerebellum of primates. I. Unilateral section of the peduncles. J. comp. Neurol., 1938, *69*, 31-46 (with E. H. Botterell [1]).

163 II. Lesions of midline structures (vermis) and deep nuclei. J. comp. Neurol., 1938, *69*, 47-62 (with E. H. Botterell [1]).

164 III. Lesions of hemispheres (neocerebellum). J. comp. Neurol., 1938, *69*, 63-87 (with E. H. Botterell [1]).

165 The Physiological Congress at Zurich. Lancet, 1938, *2*, 584.

166 Alfred Walter Campbell, M.D., Ch.M., 1868-1937. Arch. Neurol. Psychiat., Chicago, 1938, *39*, 566-568. Also under title: The late Dr. Alfred Campbell. An appreciation. Lancet, 1938, *2*, 597.

167 Postural neck reflexes in the labyrinthectomized monkey and their effect on the grasp reflex. J. Neurophysiol., 1938, *1*, 455-462 (with R. S. Dow).

168 The thalamus of the chimpanzee. III. Metathalamus, normal structure and cortical connections. Brain, 1938, *61*, 250-268 (with A. E. Walker [1]).

169 The influence of Boerhaave's *Institutiones medicae* on modern physiology. Ned. Tijdschr. Geneesk., 1938, *82*, 4860-4866.

170 Cytoarchitecture of the gorilla brain. Science, 1938, *88*, 426-427.

171 A projected *Bibliographia physiologica*. Bull. med. Libr. Ass., 1938, *26*, 148-161.

172 A note on *A world list of scientific periodicals*. Bull. med. Libr. Ass., 1938, *26*, 162-164.

1939

173 Our liberal heritage. Amer. Oxon., 1939, *26*, 10-17.

174 A style book containing suggestions for the preparation of manuscripts. J. Neurophysiol., 1939, *2*, 89-99.

175 A precis of preoptic, hypothalamic and hypophysial terminology. Res. Publ. Ass. Res. nerv. ment. Dis., 1940, *20*, 1-20 (by D. McK. Rioch, G. E. Wyshogrod, L. C. Hinsey, and D. Sheehan, edited by J. F. Fulton). *Preprint*.

176 *A bibliography of the writings of Harvey Cushing prepared on the occasion of his seventieth birthday, April 8, 1939, by the Harvey Cushing Society*. Printed for the Society, 1939, xxi, 108 pp. (with Louise Eisenhardt [1]).

177 Notes on captive *Tarsius carbonarius*. J. Mammol., 1939, *20*, 173-178 (by Norman Cook, edited by J. F. Fulton).

178 A trip to Bohol in quest of *Tarsius*. Yale J. Biol. Med., 1939, *11*, 561-574 (Cushing Anniversary Number). Reprinted Amer. Sci., 1943, *31*, 151-167.

179 Harvey Cushing's seventieth birthday. Science, 1939, *89*, 383.

180 Medical academies: past and future. N. Y. St. J. Med., 1939, *39*, 973-982.

181 An exhibition illustrating the functions of the frontal lobes. 90th Annual Session, American Medical Association, May 15-19, 1939. 22 pp. (with C. F. Jacobsen and Margaret A. Kennard).

182 Harvey Cushing and roentgenology. Amer. J. Roentgenol., 1939, *41*, 1020-1021.

183 Central levels of autonomic function with particular reference to the endocrine organs. Congr. neurol. int., 1939, *3*, 68-71.

184. Physiology of the nervous system. Science, 1939, *90*, 110.

185. Tarsiers in captivity. Nature, 1939, *111*, 514 (with H. R. Catchpole [1]).

186. Levels of autonomic function with particular reference to the cerebral cortex. Res. Publ. Ass. nerv. ment. Dis., 1939, *19*, 219-236.

187. Harvey Cushing: An appreciation. Scientific Monthly, 1939, *49*, 476-479.

188. Biography of Dr. Harvey Cushing. Bull. Hist. Med., 1939, *7*, 1127.

189. Factors in functional recovery following section of the oculomotor nerve in monkeys. J. Neurol. Psychiat., 1939, *2 n.s.*, 285-292 (with M. B. Bender [1]).

190. The physiological basis of three major cerebellar syndromes. Trans. Amer. neurol. Ass., 1939, 53-58 (with G. Connor).

191. Levels of autonomic function in the central nervous system, pp. 257-270 in: *Livro de homenagem aos Prof. A. e M. Ozorio de Almeida*. Rio de Janeiro, 1939.

192. *Harvey Cushing's seventieth birthday party, April 8, 1939. Speeches, letters, and tributes*. Springfield, Ill., Charles C. Thomas, 1939. x, 146 pp. (with Louise Eisenhardt [1]).

193. Prof. W. P. Lombard. Nature, 1939, *111*, 1084-1085.

1940

194. Dr. Harvey Cushing. Yale Univ. Libr. Gaz., 1940, *14*, 33-40.

195. Harvey Cushing: Resolutions and appreciations. Yale J. Biol. Med., 1940, *12*, 317-323.

196. Arnold Klebs and Harvey Cushing at the First International Neurological Congress at Berne in 1931. Bull. Hist. Med., 1940, *8*, 332-354 (Klebs Anniversary Number).

197. *The hypothalamus and central levels of autonomic function*. Research Publications, Association for Research in Nervous and Mental Disease. Vol. 20. Baltimore, Williams and Wilkins Co., xxx, 980 pp., 1940. (with S. W. Ranson and A. M. Frantz, joint editors).

198. Introduction: Historical résumé. Res. Publ. Ass. nerv. ment. Dis., 1940, *20*, xiii-xxx.

199. The chimpanzee in experimental medicine. Trans. Kansas City Acad. Med., 1937-39, 52-63. [issued April 1940]

200. The central nervous system. Ann. Rev. Physiol., 1940, *2*, 243-262.

201. Somatic and autonomic reflexes in spinal monkeys. J. Neurophysiol., 1940, *3*, 258-268 (with A. L. Salis [1]).

202. Late recovery of sensory discriminatory ability after parietal lesions in the chimpanzee. Amer. J. Physiol., 1940, *129*, 453 (with T. C. Ruch [1] and S. Kasdon).

203. Effect of medial lemniscus section on weight discrimination. Amer. J. Physiol., 1940, *129*, 491-492 (with E. A. Weinstein [1] and O. Sjoqvist).

204. The endocrine weights of primates. Endocrinology, 1940, *27*, 58-67 (with M. Imay [1], T. C. Ruch, and Sarah Eman).

205. J. G. Dusser de Barenne, 1885-1940. J. Neurophysiol., 1940, *3*, 283-292 (with R. W. Gerard).

206. Physiology of aviation and military preparedness. Conn. med. J., 1940, *4*, 590-594.

207. Experimental studies on the functions of the frontal lobes in monkeys, chimpanzees and man, pp. 55-77 in: *Science in progress*, 2d ser., edited by G. A. Baitsell. New Haven, Yale University Press, 1940.

208. England after the air battle of Britain. Harvard Alum. Bull., 1940, *43*, 331-333.

209. Neurology and war. Weir Mitchell Oration VIII. Trans. Coll. Phys. Philad., 1940, *8* (4th ser.), 157-165.

210. Foreword, pp. ix-x in: Cushing, Harvey, *The life of Sir William Osler*. Oxford and New York, Oxford University Press, 1940 (with W. W. Francis).

1941

211. Aspects of medical defense in England. Conn. med. J., 1941, *5*, 10-12.

212. *Fisiologia del sistema nervioso*, translated by Jaime Pi Suñer. Mexico, Editorial Atlante, 1941, xxiv, *662* pp.

213. Medicine and the sciences, chapter 8 in: *The development of the sciences*, 2d series, edited by L. L. Woodruff. New Haven, Yale University Press, 1941.

214. Notes on a recent trip to England. Amer. Oxon., 1941, *28*, 72-92.

215. John Gillies Priestley. New Engl. J. Med., 1941, *224*, 619-620.

216. Encephalization of motor functions during the evolution of the primate nervous system. Ohio J. Sci., 1941, *41*, 173-182.

217. The motor cortex in *Galago* and *Perodicticus*. J. Anat., Lond., 1941, *75*, 447-456.

218. Introduction, pp. xi-xiii in: Ruch, T. C., *Bibliographia primatologica*. Springfield, Ill., Charles C. Thomas, 1941.

219. Recent developments in aviation medicine. New Engl. J. Med., 1941, *225*, 263-268.

220. First annual report of the Historical Library. New Haven, Yale University School of Medicine, 1941. *37* pp.

221. Unsolved neurologic problems in military aviation. Trans. Amer. neurol. Ass., 1941, 112-114 (with M. W. Thorner).

222. Experimental tremor and chorea in monkey and chimpanzee. Trans. Amer. neurol. Ass., 1941, 126-130 (with Margaret A. Kennard [1]).

1942

223. Blast and concussion in the present war. New Engl. J. Med., 1942, *226*, 1-8. Reprinted, pp. 226-240 in: Pecora, W. S., ed., *War medicine*. New York, Philosophical Library, 1942.

224. Growth of primate literature since 1800. Science, 1942, *95*, 47-48 (with T. C. Ruch [1]).

225. Otfrid Foerster, 1873-1941. J. Neurophysiol., 1942, *5*, 1-17 (with M. A. Kennard [1] and C. G. de Gutierrez-Mahoney).

226. Corticostriatal interrelations in monkey and chimpanzee. Res. Publ. Ass. nerv. ment. Dis., 1941, *21*, 228-245 (with M. A. Kennard [1]).

227. Physiology and high altitude flying. With particular reference to air embolism and the effect of acceleration. Science, 1942, *95*, 207-212.

228. Development of physiology in Connecticut. Conn. med. J., 1942, *6*, 266-273. Reprinted, pp. 162-171, in: *The heritage of Connecticut medicine*, ed. H. Thoms. [Connecticut State Medical Society] 1942 (with H. E. Hoff).

229. A five-foot shelf on aviation medicine. Bull. med. Libr. Ass., 1942, *30*, 368-371 (with E. C. Hoff).

230. Medicine and air supremacy. New Engl. J. Med., 1942, *226*, 873-880.

231. Foreword, p. vii in: Rosen, G., *The reception of William Beaumont's discovery in Europe*. New York, Schuman's, 1942.

232. *A bibliography of aviation medicine*. Publication No. 5. Historical Library, Yale Medical Library. Springfield, Ill., Charles C. Thomas, 1942, vi, *237* pp. (with E. C. Hoff [1]).

233. Prospectus of a medical history of the war of 1941 to 19—. *War Medicine*, 1942, *2*, 847-859.

234. Age and reorganization of central nervous system. J. Mt. Sinai Hosp., 1942, *9*, 594-616 (with M. A. Kennard [1]).

235. Introduction, pp. v-vi in: Meeter, H. R., *Central regulation in health and disease, with special reference to the hypothalamus*. New York, 1942.

1943

236. The oestrus cycle in Tarsius. Observations on a captive pair. J. Mammal., 1943, *24*, 90-93 (with H. R. Catchpole [1]).

237. Origins of Red Cross and neutrality of wartime medical services. Conn. med. J., 1943, *7*, 253-259.

238. Arnold Carl Klebs. Yale J. Biol. Med., 1943, *15*, 645-650.

239. Functional interrelation of cerebral cortex with basal ganglia and cerebellum. pp. 201-212 in: *Essays in biology. In honor of Herbert M. Evans, written by his friends*. Berkeley, Cal., 1943.

240. Acetylcholine and the physiology of the nervous system. Science, 1943, *97*, 569-571. (with D. Nachmansohn).

241. *Physiology of the nervous system*. Second revised edition. New York, Oxford University Press, 1943. x, 614 pp.

242. Introduction. Vesalius Celebration. Yale J. Biol. Med., 1943, *16*, 106-107.

243. An exhibit arranged at the Yale Medical Library. In: *The four hundredth anniversary celebration of the* De humani corporis fabrica *of Andreas Vesalius*. Monograph 7. Historical Library, Yale University School of Medicine, pp. 53-66.

244. Anoxia, pH shifts and central nervous function. Trans. Amer. neurol. Ass., 1943, pp. 84-87. (with L. F. Nims).

245. Foreword, pp. v-ix in: Bert, P. *Barometric pressure. Researches in experimental physiology*, tr. M. A. and F. A. Hitchcock. Columbus, 1943.

246. Preface, pp. vii-ix in: Cushing, H. *A bibliobibliography of Andreas Vesalius*. New York, 1943.

247. Preface, pp. v-vi in: *The Harvey Cushing Collection of books and manuscripts*. New York, 1943.

1944

248. The Harvey Cushing General Hospital. Harvard med. Alumni Bull., 1944, *18*, 82-84. [Also privately printed, 11 pp.]

249. The nature and treatment of blast injuries. Canad. J., April 1944, *3*, 13-16.

250. William Harvey (1578-1657) and the valves in the veins. N. C. med. J., 1944, *5*, 193-194.

251. Some factors affecting the incidence of "bends" at altitude. Milit. Surg., 1944, *94*, 199-200.

252. *A bibliography of aviation medicine: supplement*. [Menasha, Wis.] (with Phebe M. Hoff [1] and E. C. Hoff).

253. Polydore Vergil, his chapters on the history of physick and his *Inuitica historia*, pp. 65-68 in: Suppl. 3, *Bull. Hist. Med.*, 1944.

254. Hand list of editions of Polydore Vergil's *De inventoribus rerum*. Compiled and arranged from a bibliography in manuscript by the late Professor John Ferguson. With an appendix on *Inuitica historia*. [Mimeographed] 1944. 15 pp. (2d. with Charlotte H. Peters).

255. Preface, pp. vii-ix in: Olmsted, J. M. D. *François Magendie*. New York, 1944.

256. The Nobel Prize in Physiology and Medicine. J. Neurophysiol., 1944, *7*, 325-326. [signed: The Editors].

257. The history of penicillin. J. Amer. med. Ass., 1944, *126*, 170-172. [unsigned editorial].

258. Foreword, pp. ix-x in: Bucy, P. C. *The precentral motor cortex*, 1944.

259. Second, third, and fourth annual reports of the Historical Library. New Haven, Yale University School of Medicine, 1944. 81 pp.

1945

260. Logan Clendening, 1884-1945. Conn. med. J., 1945, *9*, 204-205. Reprinted: J. Kans. med. Soc., 1945, *46*, 79-80.

261. *A bibliography of casual literature, 1939-1944*. Washington, D. C., Office of Scientific Research and Development. x, 117 pp. (with Phebe M. Hoff and Henrietta T. Perkins).

262. Histopathology of the central nervous system after exposure to high altitudes, hypoglycemia and other conditions associated with central anoxia. Medicine, 1945, *24*, 161–217. (with E. C. Hoff [1] and R. G. Grenell.)

263. Professor Winslow and the public health movement. Conn. med. J., 1945, *9*, 537–538. [unsigned editorial].

264. Penicillin, plasma fractionation, and the physician. Atlantic Monthly, 1945 (Sept.), pp. 107–114.

265. Appendix. The Morton and Warren tracts on ether. (Letters), pp. 176–182 in Keys, T. E. *The history of surgical anesthesia*. New York, Schuman's, 1945.

266. Fifth annual report of the Historical Library. New Haven, Yale University School of Medicine, 1945. 34 pp.

267. Men in medicine. III. Harvey Cushing, M.D. Interne, 1945, *11*, 239–242.

268. Aviation medicine, pp. 213–241 in Piersol, G. M., ed. *Cyclopedia of medicine and surgery. Reference service*. Philadelphia, F. A. Davis Company, 1945. (with E. C. Hoff.)

269. The retirement of Colonel Harold W. Jones. Bull. med. Libr. Ass., 1945, *33*, 409–412.

270. The Historical Library, 1941–1945. Yale scient. Mag., 1945, *20*, 14–16, 30–31.

1946

271. *Howell's textbook of physiology*. 15th ed. Philadelphia and London, W. B. Saunders Co., 1946. xxxv, 1304 pp. (General editor, and author of "Historical backgrounds of American physiology" and Chapters 7–9, 11–15.)

272. Art really meets medicine. Yale's exhibit finds medical artists still well ahead of surrealists. Art News, 1946, *44*, 86, 103–104.

273. The letters and libraries of Irving S. Cutter and Harvey Cushing. Quart. Bull., Nthwestern Univ. Med. School, 1946, *20*, 59–65.

274. The housing, care, and surgical handling of laboratory primates. Yale J. Biol. Med., 1946, *18*, 443–471. (with M. V. Kennard [1] and T. C. Ruch.)

275. *Harvey Cushing, a biography*. Springfield, Ill., Charles C. Thomas, 1946. xiv, 754 pp., 64 pl.

276. Sixth annual report of the Historical Library. New Haven, Yale University School of Medicine, 1946. 34 pp.

277. Medical societies and medical education. Bull. med. Soc. Cty. Monroe [etc.] (Rochester, N. Y.), 1946, *1*, 4–17.

278. Aeromedical research at Yale. Effects of high altitudes studied in decompression chamber. Yale scient. Mag., 1946, *20*, 10–12, 24. (no. 7. Apollo. (with J. F. Nims.)

279. Foreword to: *A memoir to the Academy of Sciences at Paris on a new use of sulphuric ether*, by W. T. G. Morton of Boston in the U. S. A. Presented by M. Arago in the autumn of 1847. New York, Henry Schuman, 1946. vi, 24 pp.

280. *The centennial of surgical anesthesia*. An annotated catalogue of books and pamphlets bearing on the early history of surgical anesthesia exhibited at the Yale Medical Library, October 1946. Compiled by H. F. and Madeline E. Stanton. New York, Henry Schuman, 1946. xv, 102 pp.

281. History of the Yale Medical Libraries. Bull. med. Libr. Ass., 1946, *34*, 184–188.

282. Science in American universities, 1636–1946. (Garrison Lecture.) Bull. Hist. Med., 1946, *20*, 97–111.

283. The reception in England of Henry Jacob Bigelow's original paper on surgical anesthesia. New Engl. J. Med., 1946, *235*, 745–746.

284. His vision and daring of youth; the story of the introduction of surgical anesthesia. Yale J. Biol. Med., 1946, *19*, 207–216.

285. Peacetime implications of wartime medical discoveries. Amer. Scholar, 1946, *15*, 506–515.

1947

286. Medicine today: its assets and liabilities. The Linsly R. Williams Memorial Lecture, pp. 3-26 in: *Medicine today, the march of medicine, 1946*. New York, Columbia University Press, 1947.

287. On being a literary executor. J. Neurosurg., 1947, *4*, 1-6.

288. A brief history of Yale's medical collections. Yale Univ. Libr. Gaz., 1947, *21*, 46-53.

289. The library of Arnold C. Klebs. Yale J. Biol. Med., 1947, *19*, 883-886.

290. The library of a scholar: Arnold C. Klebs. Yale Univ. Libr. Gaz., 1947, *22*, 1-6.

291. *The Sheffield Scientific School 1847-1947. A catalogue of surviving early scientific instruments of Yale College. Placed on display in the Sterling Memorial Library, October 1947*. New Haven [1947]. [12] pp. [Unsigned]

292. The vision and daring of youth: the story of the introduction of surgical anesthesia. Anesthesiology, 1947, *8*, 464-470.

293. Physiological basis of frontal lobotomy. In: Hilding Berglund Festschrift. Acta med. scand., 1947, *Suppl. 196*, 617-625.

294. Ablation of area 13 in primates. Fed. Proc., 1947, *6*, 168. (with R. B. Livingston and G. D. Davis).

295. Stimulation of area 13 and skin temperature changes following its ablation. Fed. Proc., 1947, *6*, 95-96. (with J. M. R. Delgado [1] and R. B. Livingston).

296. Interrelation between anterior lobe of the cerebellum and the motor cortex. Fed. Proc., 1947, *6*, 207-208. (with V. Soriano [1]).

297. Aviation medicine, pp. 261-285 in: Pierson, G. M., ed. *Cyclopedia of medicine and surgery. Reversion service*. Philadelphia, F. A. Davis Co., 1947. [with E. C. Hoff [1]).

298. Harvey Cushing's early training, 1887-1900. Bull. N.Y. Acad. Med., 1947, *23*, 545-558.

299. Sherrington's impact on neurophysiology. Brit. med. J., 1947, *2*, 807-810.

300. Edward Clark Streeter, 1874-1947. Yale J. Biol. Med., 1947, *20*, 203-211.

301. Preface, pp. xiii-xiv, in: Shryock, R. H., *American medical research: past and present*. New York, The Commonwealth Fund, 1947. xvii, 350 pp.

302. Harvey Cushing and Arnold Klebs: Their friendship and their libraries. Bull. Hist. Med., 1947, *21*, 512-523.

303. *Benjamin Silliman, 1779-1864, pathfinder in American science*. New York, Schuman's, 1947. xiii, 294 pp. (with Elizabeth H. Thomson).

304. Seventh annual report of the Historical Library. New Haven, Yale University School of Medicine, 1947. 36 pp.

1948

305. Second Addenda to 'A Bibliography of The Honourable Robert Boyle'. Oxford bibliogr. Soc. Publ., 1947, *n.s. 1*, 33-38.

306. Cushing 1869-1939, pp. 288-290 in: *Les médecins célèbres*. Geneva, Editions d'Art Lucien Mazenod, 1947. 371 pp. [Translated into French].

307. Benjamin Silliman and the founding of the Sheffield Scientific School. (Reprinted from *Benjamin Silliman, 1779-1864: pathfinder in American science*. New York, Henry Schuman, 1947.) Amer. Sci., 1948, *36*, 102-110. (with Elizabeth H. Thomson).

308. The surgical approach to mental disorder. McGill med. J., 1948, *17*, 133-145.

309. Introductory remarks of the toastmaster [at a farewell dinner for Dr. and Mrs. Henry E. Sigerist, The Plaza Hotel, New York, 9 May 1947]. Bull. Hist. Med., 1948, *22*, 10-11, 14-15, 18-19, *24*, *28*, 31-32, 34.

310. The Wellcome Historical Medical Museum, London. Bull. Hist. Med., 1948, *22*, 97-98.

311. The early years of Andreas Vesalius. Minnesota Med., 1948, *31*, 141-146.

312 Silliman's visit to Minnesota. Minnesota Med., 1948, *31*, 293.

313 "Cortical instability": a study of frequency effects. Fed. Proc., 1948, *7*, 74 (with R. B. Livingston [1]).

314 Harvey Cushing and his books. An address read before the Abernethian Society on July 10th, 1947. St. Bartholomew's Hosp. J., 1948, *52*, 61-64, 80-82.

315 Eighth annual report of the Historical Library. New Haven, Yale University School of Medicine, 1948. 41 pp.

316 Notes on some American medical libraries. Libr. Ass. Rec., Lond., 1948, *50*, 174-180.

317 Josiah C. Trent, 1914-1948. J. Hist. Med., 1948, *3*, 467-472.

318 Frontal lobe ablation in chimpanzees: a resumé of "Becky" and "Lucy". Res. Publ. Ass. nerv. ment. Dis., 1948, *27*, 3-58 (with M. P. Crawford [1], C. P. Jacobsen, and J. B. Wolfe).

319 Stimulation and regional ablation of orbital surface of frontal lobe. Res. Publ. Ass. nerv. ment. Dis., 1948, *27*, 405-420 (with R. B. Livingston [1], J. M. R. Delgado, E. Sachs, Jr., S. J. Brendler, and G. D. Davis).

320 Altitude decompression sickness, pp. 318-330 in: U. S. Office of Scientific Research and Development Committee on Medical Research. *Advances in military medicine* . . . Boston, Little, Brown and Co., 1948. 2 v. (Science in World War II; Office of Scientific Research and Development.)

321 *Isolation medicine in its preventive aspects. An historical survey*. London, New York, Toronto, Oxford University Press, 1948. viii, 174 pp. University of London, Heath Clark Lectures, 1947, delivered at The London School of Hygiene and Tropical Medicine.)

322 *The frontal lobes*. Research Publications, Association for Research in Nervous and Mental Disease. Vol. *27*. Baltimore, Williams and Wilkins Co., 1948. xv, 901 pp. Charles D. Aring, S. Bernard Wortis, J. F. Fulton, Eds.

1949

323 Medical progress. Neurophysiology, 1942-1948. New Engl. J. Med., 1949, *240*, 883-891; 920-927.

324 *Functional localization in the frontal lobes and cerebellum. Being the William Withering Memorial Lectures delivered at the Birmingham Medical School 1948*. Oxford, Clarendon Press, 1949. xii, 140 pp.

325 *A textbook of physiology. Originally by William H. Howell, M.D.* 16th ed. John F. Fulton, ed. Philadelphia and London, W. B. Saunders Co., 1949. xl, 1268 pp.

326 Interrelations between orbital gyrus insula, temporal tip and anterior cingulate. Trans. Amer. neurol. Ass., 1949, *74*, 173-179 (with K. H. Pribram, J. V. F. Stevenson, and P. D. Wall).

327 *Portrait bust of Harvey Cushing. Ceremonies at the unveiling, 15 January 1949*. [New Haven, Conn., The Printing Office of the Yale University Press, 1949.] [20 pp.]

328 William Osler, the humanist. (The sixth Frank Billings Lecture of the Institute of Medicine of Chicago, 25 January 1949.) Arch. intern. Med., 1949, *83*, 149-158. Also: Proc. Inst. Med. Chicago, 1949, *17*, 374-382.

329 Grace Revere Osler: her influence on men of medicine. Bull. Hist. Med., 1949, *23*, 341-351.

330 *Physiology of the nervous system*. 3d ed. New York and London, Oxford University Press, 1949. x, 666 pp.

331 The orbital gyri. Brain, 1949, *72*, 227-240 (with E. Sachs, Jr. [1] and S. J. Brendler).

332 A prolegomenon to the sciences. Isis, 1949, *40*, 99-106.

333 The discovery of the circulation. Yale sci. Mag., 1949, *23*, 3 pp.

334 William Osler as a medical historian. U. Manitoba med. J., 1949, *20*, 113-119.

345. Ninth annual report of the Historical Library. New Haven, Yale University School of Medicine, 1949. 36 pp.

1950

346. Remarks upon present-day electrocardiographic theory. Exp. Med. Surg., 1950, *8*, 288-294. (with I. Nahum [1]).
347. The brain as organ of the mind. West. J. Surg. Obstet. Gynec., 1950, *58*, 246-252.
348. Effects on gastric secretion of frontal lobe stimulation. Res. Publ. Ass. nerv. ment. Dis., 1950, *29*, 617-627. (with L. M. Davey [1] and B. R. Kaada).
349. Benjamin Silliman in his lighter moments. (Remarks at the centenary dinner of the Sheffield Scientific School, 17 October 1947.) A Chapter (pp. 185-192) from *The centennial of the Sheffield Scientific School*, G. A. Baitsell, ed. New Haven, Yale University Press, 1950. xiv, 206 pp.
350. Rabelais and his circle. Harvard med. Alum. Bull., 1950, *24*, 80-84.
351. *Humanism in an age of science, being a Ludwig Mond Lecture delivered at the Manchester School of Medicine on 6 October 1949.* Manchester, University of Manchester Press; New York, Henry Schuman, Inc., 1950. 26 pp.
352. Some notes on the Yale University School of Medicine with special reference to Milton Winternitz. Yale J. Biol. Med., 1950, *22*, 589-594.
353. *The Logan Clendening lectures on the history and philosophy of medicine. I. Vesalius four centuries later. II. Medicine in the eighteenth century.* Lawrence, Kansas, The University of Kansas Press, 1950. 52 pp.
354. The influence of European teaching on the development of American medicine. Proc. Rudolf Virchow med. Soc., N.Y., 1950, *9*, 111-122.
355. Foreword, pp. *21-23* in: *Sir William Osler: aphorisms from his bedside teachings and writings.* Collected by Robert Bennett Bean, edited by William Bennett Bean. New York, Henry Schuman, Inc., 1950. 159 pp.
356. Tenth annual report of the Historical Library. New Haven, Yale University School of Medicine, 1950. 40 pp.

1951

357. *The great medical bibliographers. A study in humanism.* (The A. S. W. Rosenbach Fellowship in Bibliography.) Philadelphia, University of Pennsylvania Press, 1951. xvi, 107 pp.
358. *Frontal lobotomy and affective behavior. A neurophysiological analysis.* (The Thomas W. Salmon Memorial Lectures.) New York, W. W. Norton & Co., 1951. 159 pp.
359. National Research Council. *Decompression sickness. Caisson sickness, diver's and flier's bends and related syndromes.* Philadelphia and London, W. B. Saunders Co., 1951. xii, 437 pp. [J. F. Fulton, ed.]
360. Textbook of physiology, 10th ed., *Tratado de fisiologia.* Translated by Jaime Pi-Suñer and Antonio Oriol Anguera. Buenos Aires, Editorial Labor, 1951. 2 vols. 1312 pp.
361. *Humanismo en una edad de ciencias.* Traduccion del Prof. Agreg. Dr. Victor Soriano. Montevideo, Editorial Garcia Morales, 1951. 16 pp.
362. Foreword, pp. vii-viii in: Sigerist, H. E., *A history of medicine.* Vol. I. New York, Oxford University Press, 1951. xxi, 564 pp.
363. Some aspects of medicine reflected in seventeenth century literature with special reference to the plague of 1665. A chapter [pp. 198-208] in: *The seventeenth century. Studies in the history of English thought and literature from Bacon to Pope.* By Richard Foster Jones and others writing in his honor. Stanford, Stanford University Press, 1951.
364. Jules Baillarger and his discovery of the six layers of the cerebral cortex. Gesnerus, 1951, *8*, 85-91. (Sigerist birthday volume).
365. Introduction [to Antibiotics issue]. J. Hist. Med., 1951, *6*, 281-286.
366. The 250th anniversary of Yale University. Nature, 1951, *168*, 636-637.
367. Yale University 250th anniversary. Brit. med. J., 1951, *2*, 962-964.

358. The impact of science on American history. (The first Stimson Lecture, Goucher College.) Isis, 1951, *42*, 176-191.

359. Corticofugal connexions of posterior orbital surface in Rhesus monkey. Brain, 1951, *74*, 66-71. (with P. D. Wall [1] and P. Glees.)

360. Lobotomy in man. Wisconsin med. J., 1951, *50*, 387-389.

361. Physiological basis of psychosurgery. Proc. Amer. philos. Soc., 1951, *95*, 538-541.

1952

362. *The frontal lobes and human behaviour*. (The Sherrington Lectures.) Liverpool, University Press, 1952. 23 pp.

363. Lewis Hill Weed—1886-1952. Yale J. Biol. Med., 1952, *25*, 214-216.

364. André Vésale, fondateur de l'anatomie moderne. Rev. Quest. sci. [Bruxelles], 1952, Sér. v, *13*, 161-170.

365. Sir Charles Scott Sherrington, O. M. (1857-1952). J. Neurophysiol., 1952, *15*, 167-190.

366. First annual report, Department of the History of Medicine. New Haven, Yale University School of Medicine, 1952. 37 pp.

1953

367. *Plan of a university*. By Ezra Stiles. Anonymous introduction by John F. Fulton and Elizabeth H. Thomson for the Fellows of Pierson College. New Haven, Privately printed at the Pierson College Press [9 June], 1953. xxiv, 24 pp.

368. *Physiologie des lobes frontaux et du cervelet. Étude expérimentale et clinique*. (Conférences Francqui.) Paris, Masson et Cie, 1953. xxii, 149 pp.

369. *Michael Servetus: Humanist and martyr*. With a bibliography of his works. New York, Herbert Reichner, 1953. 98 pp. (with Madeline E. Stanton.)

370. The historical contribution of physiology to neurology. Pages 537-544 in Festschrift volume in honor of Dr. Charles Singer. London, Oxford University Press, 1953.

371. The School of Medicine. Pages 23-24, 163-166 in: *Seventy-five. A study of a generation in transition*. A volume marking the seventy-fifth anniversary of the Yale Daily News. New Haven, Yale Daily News, 1953.

372. The place of William Withering in scientific medicine. J. Hist. Med., 1953, *8*, 1-15.

373. An introduction to "A translation of William Withering's *De animali oeconomia*" by Charles D. O'Malley. J. Hist. Med., 1953, *8*, 16-17.

374. Somatic functions of the central nervous system. Ann. Rev. Physiol., 1953, *15*, 305-328.

375. Foreword to F. H. Netter's *Nervous system*. Volume I of *The Ciba collection of medical illustrations*. Summit, New Jersey, Ciba Pharmaceutical Products, Inc., 1953. 143 pp.

376. Johannes Gregorius Dusser de Barenne (1885-1940). Pages 119-122 in: HAYMAKER, W., ed., *The founders of neurology*. Springfield, Ill., Charles C. Thomas, 1953. Also: Harvey Cushing (1869-1939). in: *Ibid.*, pages 413-417.

377. Louis Lapicque, 1866-1952. J. Neurophysiol., 1953, *16*, 95-100.

378. Arturo Castiglioni (1874-1953). J. Hist. Med., 1953, *8*, 129-132.

379. The library of Jonathan Knight (1780-1864). Yale J. Biol. Med., 1953, *25*, 468-476.

380. Gibbon, the "unpardonable undergraduate." *Antiquarian Bookman's Association Journal*, 1953, 13-18.

381. Medicine in the seventeenth and eighteenth centuries. With special reference to neurology. N. C. med. J., 1953, *14*, 261-267.

382. Michael Servetus and the lesser circulation of the blood through the lungs. Pages 62-71 in: *Initium de Michel Servet et de Sebastien Castellion*. Bourbon-le-Duc, Floch, Willaut & Zoon, 1953.

383. Die neuromuskulare Übertragung. Eine historische Übersicht. Wien. med. Wschr., 1953, *103*, 418-420.

384. History of medical education. Brit. med. J., 1953, *2*, 457-466.

385. Medicine, warfare, and history. J. Amer. med. Ass., 1953, *153*, 482-488. Reprinted in U. S. Armed Forces Medical Journal, 1953, *4*, 1703-1718 and pages 427-441 in: *The Smithsonian Report for 1954*, 1955.

386. The limbic system: a study of the visceral brain in primates and man. Yale J. Biol. Med., 1953, *26*, 107-118.

387. Notes on the history of the postural reflexes. Folia psychiat. (Amst.), 1953, *56*, 455-459.

388. Antoine Laurent Lavoisier's "Réflexions sur les effets de l'éther vitriolique et de l'éther nitreux dans l'economie animale." J. Hist. Med., 1953, *8*, 318-323. (with D. I. Duveen and H. S. Klickstein).

389. A bibliography of Galvani's writings on animal electricity. Pages 157-176 in *Luigi Galvani, commentary on the effects of electricity on muscular motion*. Translated into English by Margaret Glover Foley. I. Bernard Cohen, Editor. Norwalk, Connecticut, Burndy Library, 1953. (with Madeline E. Stanton).

390. Ramón y Cajal et la neurophysiologie. Act. Ibuso-esp. Neurol., 1953, *12*, 211-217.

391. Second annual report, Department of the History of Medicine. New Haven, Yale University School of Medicine, 1953. 28 pp.

1954

392. Contemporary concepts of the hypothalamus and their origin. Stephen Walter Ranson Memorial Lecture. Quart. Bull. Nthwest. Univ. Med. Sch., 1954, *28*, 10-16.

393. Ralph Linton, 1893-1953. Yale J. Biol. Med., 1954, *26*, 313-316.

394. Miguel Ozorio de Almeida, 1892-1953. J. Neurophysiol., 1954, *17*, 92-93.

395. Recent advances in neurophysiology. J. Neurosurg., 1954, *11*, 1-6.

396. Harvey Cushing as we knew him. Bull. N.Y. Acad. Med., 1954, *30*, 887-901.

397. Samuel Clark Harvey, 1886-1953. Bull. Hist. Med., 1954, *28*, 275-276.

398. Indirect spinal cord injuries due to gunshot wounds of the spinal column in animal and man. Milit. Surg., 1954, *111*, 253-265. (with W. W. Klemperer [1], Harold Lamport, and M. G. Schorr).

399. An experimental critique of the effects of anterior cingulate ablations in monkey. Brain, 1954, *77*, 34-44. (with K. H. Pribram [1]).

400. Third annual report, Department of the History of Medicine. New Haven, Yale University School of Medicine, 1954. 26 pp.

401. Samuel Clark Harvey. The Century Association Year book, 1954, pp. 153-154.

402. Preface, pp. IX-X in: Riedman, Sarah. *The world through your senses*. New York, Abelard Schuman, Inc., 1954. 208 pp.

403. The influence of British and Continental teaching on early American medical schools. Emory Univ. Quart., 1954, *10*, 160-167.

404. Foreword in: Buxton, R. J. *Doctors in the sky*. Springfield, Ill., Charles C. Thomas, 1954. 326 pp.

405. Preface, pp. v-viii in: Duveen, D. I. and Klickstein, H. S. *A bibliography of the works of Antoine Laurent Lavoisier, 1743-1794*. London, Wm. Dawson and Sons, Ltd. and E. Weil, 1954. 491 pp.

1955

406. Louis H. Bauer and the rise of aviation medicine. (First Louis Hopewell Bauer Lecture.) J. Aviat. Med., 1955, *26*, 92-103.

407. Fourth annual report, Department of the History of Medicine. New Haven, Yale University School of Medicine, 1955. 24 pp.

408. *Textbook of physiology*. 17th ed. Philadelphia, W. B. Saunders Co., 1955. 1275 pp. (John F. Fulton, ed.)

John F. Fulton and Yama, an early member of the primate colony

(Photograph by Richard U. Light, 1933)

J.F.F. in the Laboratory of Physiology Library surrounded by some of the books in his collection subsequently given to the Yale Medical Library

(Photograph by Richard U. Light, 1933)

Operating with Morris B. Bender, 1936-37

J.E.E. (at left) operating as a regular teaching procedure before a class in physiology

King Léopold of Belgium greeting the Francqui Professor during his lectureship at the University of Louvain, September—December, 1951

With a group of Laboratory associates on the steps of the Yale School of Medicine, 1952 *Back row:* J. F. F. and Eric A. Turner (England). *Front row:* Robert B. Livingston (U. S.), Bal Krishan Anand (India), Jose M. R. Delgado (Spain), Hsiang Ting Chang (China), and Rajinder S. Sikand (India)

(From a kodachrome by Dr. Delgado)

J.F. and Lucia Fulton after the London wedding in August 1955 of one of the three British children who came to them during the early days of World War II

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THE FUTURE OF NEUROLOGY

Among those clinicians who studied with John Fulton there were some who went to his laboratory to further their training in an era when neurophysiology was considered to be the dynamic basic science for neurology and neurosurgery. There it was hoped to obtain a foundation which taken together with neuroanatomical and neuropathological knowledge might sharpen diagnostic skill, and perhaps even make for a certain investigative bent. At Yale, clinicians pure and simple were immersed in a sea of physiology—neurological as well as general—such as required them to swim or sink. Fortunately, there were always at hand those colleagues who, it was realized later, were significant persons in one's life, with whom it was possible to test out growing conceptions of this basic science; it was a Fultonian forte to be surrounded by persons of wit, fascination, and good will, whose collaboration was ever available.

The permeation of the atmosphere with books, books, and more books, and the unassuming historical approach must have been responsible for the broadening of many an uncommitted young man. This never to be forgotten educational experience was leavened by a charming concern with the social side, and evenings at Mill Rock were hardly less important than the days in the laboratory. Visitors of great moment were the "piece de résistance," day and night.

Finally, there was sensed the continuing interest in one's career; the mere fact of leaving did not sever connections with the Laboratory. What I have had to say so far depicts in many ways an ideal in educational opportunity. There is the subject and the room to achieve it, the friends, the philosophy, the humanity and warmth surrounding it. The handling of ideas I will leave for later. Because of this type of neurophysiological exposure some of us became dynamic neurologists and neurosurgeons, improved diagnosticians certainly, and better equipped to teach the subject if ever we had in us any of the talents of the teacher.

There would be general consent, I believe, that the Laboratory of Neurophysiology at Yale under Fulton played a significant part in molding present neurology. This is not the place to review the researches and con-

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cepts that have stemmed from this school of basic science and their effect upon the clinical discipline. They are generally well known. But in light of the influence of this laboratory on current neurology, it would not seem amiss to say a few words about future neurology.

In one of his provocative addresses, Sir Francis Walshe,[1] the omnipresent critic of the neurological scene, recently propounded his views about the future of neurology before the Royal Society of Medicine. There is no need to dwell on Sir Francis' function as the gadfly of neurology—a troubler of the waters, as he terms it—nor to recall that the gadfly stirs up a lackadaisical herd, though this be a secondary function. Sir Francis takes us to task because the neurophysiologically-oriented clinician has contributed little to understanding of the etiology and pathogenesis and less to the cure and prevention of neurological disease. The liberal pursuit of knowledge—the prime endeavor of the anatomist and physiologist—does not allow for much interest in morbid categories, which are or should be the primary concern of the neurological clinician. The clinician with neurophysiological bent seems to be hindered rather than helped in his search for practical means; Sir Francis implies that the product is before us to be seen by all who will but take the trouble to look.

And Sir Francis, in his considerably greater rôle of synthesis, proposes as a remedy for our ignorance of the nature and etiology of many common neurological diseases that some neurologists be trained in biochemistry, enzyme chemistry, and metabolism where the major harvests are now being reaped. Toward this he recommends that the Medical Research Council arrange for scholarships which allow the trained young clinician of promise to obtain three years' training in a scientific discipline relevant to the field of work he intends later to cultivate as a clinician, the last year being given to the application of what has been learned to clinical problems.

While I don't presume to read Sir Francis' intent, I venture to suggest that he has once again focused his searching mind on a single aspect of the subject for emphasis. He is not inclined to throw out the baby with the bath. He would subscribe to the proposition, I am sure, that the anatomical, physiological, and pathological orientation of the clinical neurologist is a requisite because modern neurology is manifestly the application of these basic sciences to diagnosis. Few specialties require of its practitioners such concentration on its basic sciences as does neurology. I envision no immediate change in this method in the making of excellent clinicians.

Heretofore and even today one could safely ignore all that is chemistry and still become a facile diagnostician though, as it seems Sir Francis has demonstrated, contribute little or nothing to revelation. While there will be agreement that clinical neurology should be in closer contact with biochem-

ical research, the proposition to train one person in both disciplines is not likely to be attractive to many recruits. Up to now advances in general medicine via biochemistry have been made by chemists and not by physicians working in chemistry. To become proficient in neurology, let us say, at a high academic level is currently so onerous and time consuming that relatively few attempt it. Yet there is little doubt that the man with knowledge of the physical and chemical activity of the brain will play an increasingly important part in the study of its disturbances, including those of thought.

It seems that neurology is a much broader discipline than the practice of it and will require for its advancement more manpower or better brain power than the neurologist can bring to it. There is so much to encompass in the making of a topflight neurologist or biochemist that currently, at least, the proficiencies of one are out of the range of the other. Such differentiation as is demonstrated by the trained neurologist or biochemist must be followed by progressive integration, as John Hughlings Jackson said for the nervous system long ago. But there is no reason why research biochemists should not share as equals the clinical facilities of hospitals, and, as we know, this has been occurring in some cases.

In an address before the American Philosophical Society, Vannevar Bush[5] surveyed the scientific scene and addressed some remarks to our problem. He listed a few of the recent advances in biochemistry and stated that the discipline was in its infancy and that it furnished an exceedingly attractive field for men of courage and fertile minds. He also noted that this held true for psychology, which for our purposes he may as well have termed neurology. Bush said that where these disciplines meet to attempt an attack upon the brain processes of man, there is a situation comparable to that in evolution before Darwin; many of the essential notions have been or are being excavated, but the critical syntheses all still lie ahead. He continued the parallel between the evolution of science and organic evolution with the statement that the former is a radiating evolution, producing new species of science almost daily. "There is intense specialization to fill niches in the environment. Certain species have specialized to the point where they have lost contact with the main thread—perhaps have lost their capacity for adaptation (p. 32)."

What a wonderful argument for progressive integration, for the working together of men variously trained! It would not seem plausible except in the most unusual case to expect the single person to have more than one "intense specialization," and I submit that neurology with its required basic sciences—required so that a man may become an able diagnostician or teacher—is a single intense specialization, and that the newer biochemistry

is another and something entirely apart, and there are many more for which a mutation has not yet produced an adequate substitute. Perhaps, to continue the analogy with evolution, in time and according to the Walshian plan a mutation will occur, but it would seem an unlikely happening.

Bush brings forward another factor that is bound to affect all scientific endeavor—the aids to man's thinking represented by the analytical machines. He noted that:

> One can conceive an analogue machine that could handle the routine of organic chemistry far better than a man could do. It could have a far more extensive and accurate memory. It could manipulate relationships far more rapidly and with greater and more accurate restraints than a human brain. It could even learn by experience if necessary. . . . It is possible, on paper at least, to build a machine which will proceed from item to item by principles of association, as does the brain, without pyramidal indexing. There is no reason why man should not relegate to the machine all those parts of his thought processes which are repetitive or subject to precise formulation. . . . In fact he must do so if he is to handle all the mass of data he is creating (p. 32).

So it would seem, too, that there could be an exciting future for the neurologist interested in electronics, and so it goes from one field of intense specialization to the other.

The unitary approach to neurology—be it neurophysiological or biochemical or any other—is as apt to be fallacious as has been the unitary approach to any single disease; perhaps this is a point that Sir Francis Walshe is striving to make. I submit that no one can tell whence progress may come, and while it is useful to call attention to what we consider to be fallacious approaches, it is well to be humble while doing it. In relation to the overwhelming amount there is to know at the present time, any single person's holding in the knowledge market is bound to be meager. This, too, points toward progressive integration as an approach, a maneuver which interestingly enough requires as much of the feelings as it does of intelligence. Behavior is ever with us, and quite obviously we cannot know too much about it.

It should be apparent throughout this essay that I am discussing only the best there is to be had for neurology, as certainly was the case in Sir Francis Walshe's presentation. Our concern with the advancement of neurology and particularly with research, as well as the neurophysiological approach which he looks upon as outmoded, implies the function of good minds. The fillip lent neurology by methods akin to those in vogue in the advertising field will not help; in no case may quantity be expected to perform the functions of quality.

As Bush has said:

> It appears that science needs new methods as it approaches problems which reach beyond the simple relations on which much of its present success has been built. These methods will involve new ways of storing and consulting the record, no doubt. But they will involve also new patterns of collaboration where several highly specialized disciplines, beyond true mastery of any individual, are essential for full insight. We can proceed effectively on many of the paths now open only when we learn to interrelate the thought patterns of allied minds with far more intimacy than is now furnished by books, lectures, or seminars. As this occurs the ways in which a scientist will proceed about his business, the ways in which youth will be trained, the position of science in society will be altered greatly (p. 32).

There will be some who will bring up the now hackneyed argument that medicine is not a science, a proposition that has become nearly self evident. But the words apply nonetheless to our artistic science. It makes us feel better when Bush refutes the formulation of a code of ethics from a mechanistic universe which, some recent writers have seemed to think, followed in logical sequence.

> This code, in summary, is very simple. Man controls his destiny; let him so control it as to build for himself a better life . . . This is to assert that there is no reality beyond those things which we can measure with a rule as time by a clock and that value can be deduced from a statement of fact. But man's motivations emerge from his entire experience. The seat of ethics is in our hearts, not in our minds (p. 33).

As likely to be as useful as the research man in the conquest of disease is the teacher who handles adeptly the sensitive mind of some of his young charges and who is not afraid of new ideas. This, of course, is the long view which requires the evaluation of teachers as the equivalent of those dedicated primarily to research, a rather unlikely commitment in these times. Again we would like them both rolled into one, the researcher and the teacher. But again we deal with two areas of intense specialization, though in this case they are less likely to be so mutually exclusive. This is one of the marvelous blends that occurs with just enough frequency to make us ever hopeful, though it is not an easy mixture, its frequency being considerably more apparent than real. Very few worthwhile human endeavors have been more often impersonated than that of being a teacher, one need only review one's own experience as a student to savor this point.

Then there is the ability to handle ideas. Wilfred Trotter, among the greatest of medical philosophers, commented on this feature of our culture as follows:

. . . if mankind is to profit freely from the small and sporadic crop of heroically gifted it produces, it will have to cultivate the delicate art of handling ideas. Psychology is now able to tell us with reasonable assurance that the most influential obstacle to freedom of thought and to new ideas is fear; and fear which can with inimitable art disguise itself as caution or sanity or on occasion even as courage (p. 30).

Such heavy handedness has not been so much of a problem as it was formerly. With the general loosening of discipline of one sort or another that has been occurring, ideas though just as rare are not quite so vulnerable; the modern cat dares more than look at a king.

During John Fulton's professorship in physiology, he was a fine practitioner of Trotter's "the serene sanity which is the scientific mind," since he gave to every fresh idea its one intense moment of cool but imaginative attention before venturing to mark it for rejection or suspense. He was ever aware that youth must be encouraged to think for itself and that one of the functions of the good teacher is that of treading gently, though not flabbily, when dealing with developing minds. Teacher, investigator, and handler of ideas, all of these were the concern of John Fulton the physiologist. In these several roles he has had as much to do with neurology present as any modern physiologist, and it is a good wager that via his pupils he will have much to do with future neurology. And his encouragement of patterns of collaboration, among highly specialized disciplines and people, is apt to be the method of the future whereby neurological revelations will be derived.

REFERENCES

1. Bush, V.: For man to know. The Atlantic Monthly, 1955, *196*, 29-34
2. Trotter, W. *The commemoration of great men. The collected papers of Wilfred Trotter, F.R.S.* London, Oxford University Press, 1941. 194 pp.
3. Walshe, F. M. R.: The future of neurology. Proc. roy. Soc. Med., 1955, *48*, 120-124.

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THE OXYGEN CONCENTRATION GRADIENT BETWEEN THE PLASMAS IN THE MATERNAL AND FETAL CAPILLARIES OF THE PLACENTA OF THE RABBIT‡

The observations that form the substance of this report deal with circumstances associated with the transfer of oxygen across the haemochorial placenta of the rabbit. They were made in an effort to expand our knowledge of the comparative physiology of the exchange of the respiratory gases between mother and fetus with particular reference to the effects upon this exchange wrought by variations in placental structure, such as the number of tissue layers that separate the fetal and maternal plasmas through which the respiratory gases must diffuse. In the mature placenta at the end of gestation the number of these tissue layers is said to vary from one to six depending upon the animal groups under consideration.[1] According to Grosser's classification there are six in the horse and pig, five in ungulates, sheep, and goats, four in the dog and cat, three in the human and the rabbit, though at the very end of the gestation period there is, in some parts of the rabbit placenta, but one separating layer.[2]

As a first approach to this broader problem, a study was made of the transfer of oxygen across the five layered "syndesmochorial" placenta of the sheep.[3] The results indicate that there is an oxygen pressure gradient of about 40 mm. Hg between the maternal and fetal plasmas which is maintained relatively constant over the greater part of the gestation period (56–137 days, full term *circa* 145 days). As the oxygen pressure in the blood returning to the placenta via the umbilical artery appears to range between 10 and 20 mm. Hg, the minimum unloading pressure in the uterine vein must vary between 50 and 60 mm. Hg, a pressure range at which the maternal blood of the sheep is 60% to 70% saturated with oxygen. Maintenance of this steep gradient across the five layered placenta limits the

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fraction of the total oxygen brought to the placenta by the maternal blood that can reach the fetus.

The experiments described here were carried out in an effort to obtain comparable information about conditions in the rabbit that would permit an assessment of the limitations put upon the oxygen transfer by the thinner placenta. In the earlier studies on the placental transfer of oxygen in the sheep, the oxygen pressure as estimated by relating the percentage saturation of the hemoglobin in a given blood sample to an appropriate dissociation curve was used to express the force driving the oxygen across the placental barrier, as if that barrier were comparable to the pulmonary epithelium and the oxygen moving from a gas phase into solution in a liquid. In point of fact, when two liquid phases are involved, as in the movement of oxygen from the plasma across the capillary wall into the tissue fluid (or as in the placenta or across the tissue capillaries of the brain, muscle, etc.), it is the difference in the concentrations of the oxygen molecules, i.e., the difference in the number of oxygen molecules in a given volume on either side of the barrier across which the net transfer of oxygen is taking place, that is related to the effective force. Accordingly, we have expressed the values for the oxygen content of our plasma samples in this study in terms of its concentration. Since the concentration of oxygen, $_cO_2$, in plasma at 38° C. can be expressed by the equation

$$_cO_2 = a\ _pO_2$$

where a is the solubility coefficient at that temperature and $_pO_2$ the oxygen pressure in a gaseous phase with which the plasma of whole blood would be in equilibrium, the units of pressure on the abscissa of the oxygen dissociation curve of whole blood—as usually drawn (Figs. 1, 2, and 3)—can be converted for our purpose to concentration (millimols per liter) by multiplying them by a or 0.00135; the points on the abscissa then represent the oxygen concentration in the plasma with which the hemoglobin in the corpuscles is in equilibrium at varied percentage saturations and are to that extent a more accurate representation of facts that are implied when the gas pressure is plotted on the abscissa. Moreover, the representation is one that permits the ready estimation of the oxygen concentration in the plasma of any blood sample by the reference of the percentage saturation of its hemoglobin to an appropriately constructed dissociation curve and it is, accordingly, most useful for our purpose. For comparison we have presented the dissociation curves we obtained with pressure plotted on the lower abscissa (Figs. 1, 2, 3). For the estimation and illustration of concentration gradients Figure 4 is drawn with concentration on the lower abscissa.

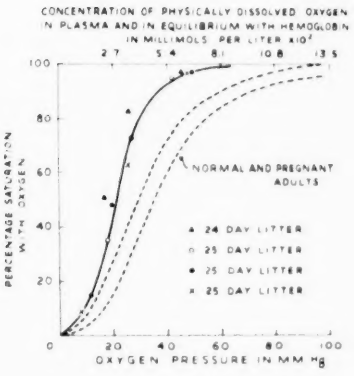

FIG. 1

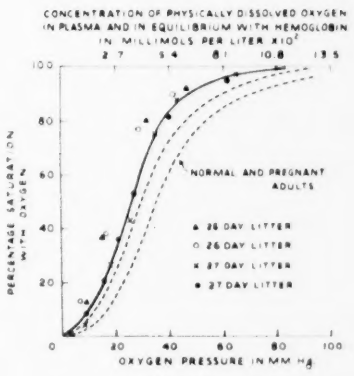

FIG. 2

FIG. 1. Oxygen dissociation curve of the pooled blood of a litter of 25-day rabbit fetuses. The individual points represent the degree of saturation at specific oxygen pressure of samples of pooled blood of litters of ages that are indicated in the key. The two broken curves limit the area in which the points obtained with blood of adults—pregnant and nonpregnant—fall.

FIG. 2. The oxygen dissociation curve is drawn through points obtained with pooled bloods of litters 27 days' gestation age. As indicated in the key the other points were obtained with bloods from litters of 26 days. The broken curves limit the adult fields as in Figure 1.

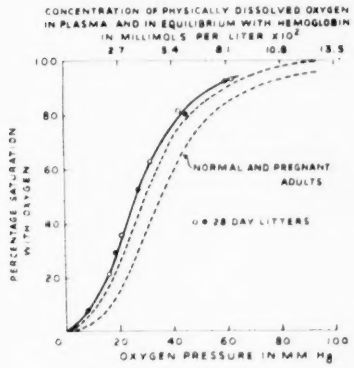

FIG. 3

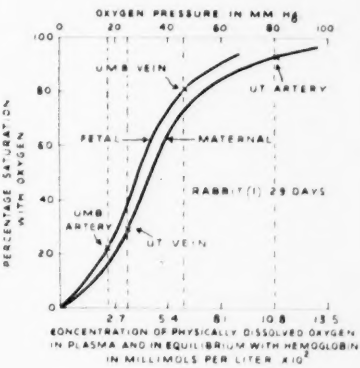
OXYGEN PRESSURE IN MM Hg
UMB VEIN
UT ARTERY
FETAL
MATERNAL
RABBIT (I) 29 DAYS
UMB ARTERY
UT VEIN
PERCENTAGE SATURATION WITH OXYGEN
CONCENTRATION OF PHYSICALLY DISSOLVED OXYGEN IN PLASMA AND IN EQUILIBRIUM WITH HEMOGLOBIN IN MILLIMOLS PER LITER X10²

FIG. 4

FIG. 3. The oxygen dissociation curve as the key indicates was prepared with the pooled blood of 28-day litters. The broken curves limit the adult field as in Figures 1 and 2.

FIG. 4. The pair of dissociation curves—maternal and fetal—and the four points on them serve to illustrate how the degree of saturation of each of the individual samples drawn from the four placental vessels was related to the curve and how the point on the curve was used in turn to estimate the oxygen pressure and oxygen concentration in the plasma of the samples. For further explanation see text.

In the rabbit[1] as in the sheep[2] the fetal and maternal bloods flow through the placenta in more or less parallel capillary systems in opposite directions, that is to say, the blood leaving the placenta via the umbilical vein is approaching equilibrium with that entering in the maternal artery and the blood entering the uterine veins from the placenta with that in the umbilical artery. Accordingly, the difference in the oxygen concentration in the plasmas at the arterial end of the placenta was estimated by subtracting the value for the blood of the umbilical vein from that for the blood in the uterine artery, the difference at the venous end by subtracting the plasma concentration in the umbilical artery from that of the uterine vein. These differences are expressed in terms of pressure to permit them to be compared with data already in the literature, and in concentrations for the reasons outlined above. The average difference in plasma oxygen concentration between the maternal and fetal bloods—that uniform concentration difference which would result in the transfer of the same quantity of oxygen between the maternal and fetal capillary beds per unit time as is transferred by the varying concentrations that exist along their length—was estimated by first determining the average pressure gradient as was done in the case of the sheep,[2] for the larger values of pressure are more convenient to work with than those of concentration. The concentration gradient was then obtained by multiplying the pressure number by a, whose value is 0.000135 millimols of oxygen per liter per mm. Hg for plasma at 38° C.

MATERIALS AND METHODS

The does for these experiments were large New Zealand Whites purchased from Mr. D. A. Whetstone of West Haven, Connecticut, who provided their breeding dates as well; without his interest and assistance this important information would have been difficult to obtain. The animals were anesthetized with intravenous Nembutal—0.5 cc. per kilo.

The blood for the oxygen dissociation curves of the normal rabbits was drawn, after they had been anesthetized, from the femoral artery into a syringe containing an oxalate fluoride mixture; the final volume was adjusted to contain nine parts of blood and one part of that mixture. Where necessary, the results were corrected for dilution. The dissociation curves of the bloods of the pregnant does were prepared with blood similarly drawn from the aorta after blood had been obtained from the fetuses. The blood for the fetal dissociation curves was drawn from the umbilical vein into 2 or 3 cc. tuberculin-type syringes whose walls had previously been moistened with a neutral heparin fluoride solution that was driven out through the needle—usually of 24 or 27 gauge. The samples were pooled for the construction of the curves.

The oxygen dissociation curves of the blood of the adults were prepared after the manner described earlier for the sheep's blood,[2] but the volume of blood available for

the construction of the fetal curves was too small to be so treated. Hence we fashioned an inner cylinder that fit inside the large tonometers. The narrow neck of this cylinder passed through the stopper closing the end of the tonometer. This narrow neck was in turn closed with a small rubber stopper. After the gas mixture in the tonometer had been prepared in the usual manner by evacuation and replacement the blood was introduced into and later withdrawn from the inner cylinder by means of a hypodermic needle thrust through the smaller stopper. The pH of the bloods was determined with the glass electrode before their equilibration and the carbon dioxide content of the gas mixture was so adjusted that except where noted the bloods were at equilibrium pH 7.4 ± 0.01. These determinations made at room temperature were corrected to 38° C. using Rosenthal's factor.

The blood used in the estimation of the percentage saturation and the oxygen concentrations of the bloods entering and leaving the fetal and maternal sides of the placenta were drawn in circumstances in which special precautions were taken to ensure that the samples as they were drawn were representative of normal conditions *in utero*. The pregnant does were anesthetized with Nembutal; the animal was then so placed that the abdomen was fully immersed in a large bath containing Ringer's solution held at 40° C. by means of a thermoregulator and heater. The Ringer's was gently agitated by bubbling air through it. When the uterus was delivered after laparotomy into the Ringer's, its musculature was quite inactive, and the color of the blood in the uterine vessels did not alter visibly during the course of the experiment. The sample of maternal venous blood was drawn from one of the conveniently oriented uterine veins draining the horn containing the fetus to be studied. The fetal vessels were then exposed by a small incision at right angles to the long axis of the uterus and just above the umbilicus. The fetus was not removed from the uterus; the membranes covering the placenta were cleared away and the branching umbilical vessels were traced to its surface. A favorably situated tributary of the umbilical vein was selected and 0.3-0.4 cc. was withdrawn via a no. 27 needle into a tuberculin-type syringe whose walls had been moistened with a heparin fluoride solution. Next, a sample of approximately the same size was similarly withdrawn from one of the umbilical arteries. Particular attention was paid to the color of the placental vessels as the samples were drawn; if any change in color was noted, the samples were discarded. Samples were drawn from but one fetus in each litter. These rather rigid standards reduced the number of samples available for analysis, but their adoption appeared to be essential to insure the representative character of the samples drawn. The last maternal sample was drawn from the central artery of the ear.

After the samples were drawn, the syringes containing them were capped and put into an ice water bath. The oxygen contents and capacities of the samples were determined by Mason's method for small samples with this modification, the samples were transferred directly from the syringe to the measuring pipette.

The oxygen concentrations in the fetal blood samples were estimated by referring the percentage saturation of each one to a dissociation curve prepared at pH 7.4 ± 0.01 from the pooled blood of a litter of the same age (see Fig. 4). Any possible difference in pH was neglected. The saturations of the maternal samples were similarly referred to curves prepared at pH 7.4 ± 0.01 with blood taken from the aorta at the end of the experiments.

RESULTS

Oxygen dissociation curves of maternal and fetal blood. The oxygen dissociation curves of maternal and fetal blood prepared at pH 7.4 ± 0.01 with blood drawn from the aortae of ten female rabbits that were not pregnant and had not recently been so fell when plotted within the area limited by the broken lines, so indicated in Figure 1. The points on the dissociation curves similarly prepared with bloods from 23 pregnant does sacrificed at stages in gestation from the 24th to the 30th day post-insemination fell within this same area, whereas the points that form the bases for the fetal curves tend to lie to the left of it (Figs. 1-3).

The three points determined with the blood of a 24-day litter—see Figure 1—indicate that the oxygen dissociation curve tends to be hyperbolic at this age; the blood attains a saturation of 97% at an oxygen pressure of only 46 mm. Hg. With advancing fetal age the curve becomes progressively less hyperbolic and more sigmoidal until at term—30 days—the individual points that describe the curve are distributed along or in the left margin of the area that embraces the adult curves. This gradual change in the character of the dissociation curve and in the affinity of the fetal blood for oxygen is well illustrated by the decrease in the degree of saturation when equilibrated with an oxygen pressure of 40 mm. Hg as gestation advances. At 24 days the blood is *circa* 95% saturated; at 26 days the saturation has fallen to 88% at that pressure, and by the 28th day to about 76%. The saturation of the blood of the adult females ranges between 58% and 68% when the oxygen pressure in the tonometer is 40 mm. Hg and the pH 7.4 ± 0.01.

The variability in the distribution of the points obtained, using bloods from different litters of the same age, is illustrated in Figures 1, 2, and 3. The range of variation was rather less than had been expected; the points obtained with different bloods and oxygen pressures may be combined to form a curve with a degree of deviation not much greater than would result from the use of points obtained from a single individual. The variations in individual development within a litter which must surely exist appear to have cancelled each other out.

This limited range in the variability of the degree of saturation obtained when pooled bloods of litters of the same age were exposed to the same oxygen pressure encouraged us to use the composite fetal curves in the estimation of the oxygen concentrations—as reflected by the percentage saturation—in the small samples that might be drawn from the umbilical vessels of individuals of other litters of the same age. The errors so introduced did not appear to be any greater than those inherent in the sampling

of the blood in these vessels. In the estimation of the oxygen concentrations in the bloods from the umbilical vessels of fetuses 30 days' gestation age, we used curves prepared with the pooled blood from the litter mates drawn after the umbilical samples.

Oxygen concentration gradient between maternal and fetal bloods. Estimation of the oxygen concentrations in the fetal and maternal bloods entering and leaving the placenta were made on five individuals. One was 27 days' gestation age, another 28; two were 29 day fetuses and one a 30-day fetus. In each case the oxygen content of the sample as drawn was determined together with the oxygen capacity; these two values were used to calculate the degree of saturation. Thus the oxygen content of the blood drawn from the umbilical vein of the fetus 27 days old was 10.4 volumes per cent and the oxygen capacity 12.4; the saturation was 10.4/12.4 or 84.2%. Reference to the composite dissociation curves for bloods from 27-day litters indicates that an oxygen pressure of 39 mm. Hg is required to produce that saturation; thus, the O_2 concentration in the plasma of the vessel from which the sample was drawn was that concentration which would exist in a plasma equilibrated with an atmosphere containing O_2 at a pressure of 39 mm. Hg, or an oxygen concentration of 39 x 0.00135 = 0.0526 millimoles/liter. The oxygen plasma concentration in each blood sample was similarly estimated; the values are presented in Table 1.

As the blood leaving the placenta via the umbilical vein is last in opposition to the maternal stream entering via the uterine artery, the O_2 concentration gradient between the arterialized bloods—fetal and maternal—can be estimated by subtracting the O_2 plasma concentration of the umbilical vein sample from that of the uterine artery. Similarly, the concentration gradient at the venous ends of the placental capillaries, where the blood leaving the placenta by the tributaries of the uterine vein is opposed by fetal blood from the umbilical artery, is represented by the plasma oxygen concentration difference between the former and the latter. The results of these estimations are also given in Table 1, in the column M_1O_2-F_2O_2. The upper figure of each pair is the plasma oxygen concentration difference between the uterine artery and the umbilical vein; the lower figure represents the same difference between uterine vein and umbilical artery. At the arterial end of the placental capillaries the plasma oxygen concentration differences for the five individuals studied varied between 0.072 and 0.047 millimoles/liter plasma; the concentration difference at the venous ends (uterine vein-umbilical artery) ranged between 0.004 and 0.012 millimoles/liter.

TABLE I. DATA OBTAINED ON BLOOD SAMPLES DRAWN FROM THE PLACENTAL VESSELS

Fetal age in days	Placental vessel	Oxygen capacity vols %	Oxygen content vols %	S_t Sat.	Est. $_pO_2$	Est. $_cO_2$ mmols/liter x 10^6	M_pO_2 - F_pO_2	M_cO_2 - F_cO_2 mmols/liter x 10^6	Average Diff. $_pO_2$	Average Diff. $_cO_2$ mmols/liter x 10^6
27	Ut. A.	12.7	12.2	96.0	92.0	12.425	53.0	7.160		
	Umb. V.	12.4	10.4	84.2	39.0	5.265			9	1.215
	Ut. V.	12.7	2.5	19.2	19.0	2.565	3.0	0.405		
	Umb. A.	12.4	3.2	24.0	16.0	2.160				
28	Umb. A.	12.4	11.8	95.5	91.0	12.285	50.5	6.818		
	Umb. V.	13.5	10.7	79.1	40.5	5.467				
	Ut. V.	12.4	3.7	29.8	25.0	3.375	11.0	1.485	14	1.890
	Umb. A.	13.5	2.3	17.5	14.0	1.890				
29	Ut. A.	17.9	17.0	94.5	90.0	12.150	43.0	5.805		
	Umb. V.	16.3	13.6	83.4	47.0	6.345			10.5	1.417
	Ut. V.	17.9	4.7	26.2	22.0	2.970	6.0	0.810		
	Umb. A.	16.3	3.1	19.0	16.0	2.160				
29	Ut. A.	13.3	12.2	92.0	80.0	10.800	35.0	4.725		
	Umb. V.	13.2	10.7	81.0	45.0	6.075			10.0	1.350
	Ut. V.	13.3	3.9	29.4	25.0	3.375	8.0	1.080		
	Umb. A.	13.2	2.7	20.6	17.0	2.295				
30	Ut. A.	15.1	14.2	95.0	90.0	12.150	42.0	5.670		
	Umb. V.	15.6	12.8	82.3	48.0	6.480			8.0	1.080
	Ut. V.	15.1	4.4	29.0	25.0	3.375	6.0	0.810		
	Umb. A.	15.6	3.6	23.3	19.0	2.565				

M_pO_2 is maternal partial pressure of oxygen.
F_pO_2 is fetal partial pressure of oxygen.

M_cO_2 is maternal concentration of oxygen.
F_cO_2 is fetal concentration of oxygen.

The average plasma oxygen concentration gradient along the two sets of placental capillaries has been estimated in each one of the five cases. The average pressure difference, as estimated by the method mentioned earlier, ranged between 8 and 14 mm. Hg; accordingly the average concentration difference ranged between 0.011 and 0.019 millimoles/liter. The individual values for both average oxygen pressure and the oxygen plasma concentration gradient found in each case are listed in Table 1.

DISCUSSION

The average concentration difference across the rabbit placenta (0.011–0.019 millimoles/liter) contrasts sharply with that which appears to exist across the placental barrier in the sheep. The average oxygen pressure difference between the maternal and fetal bloods in the sheep was *circa* 40 mm. Hg indicating an oxygen plasma concentration gradient of 0.054 millimoles/liter.

It is tempting to associate this difference in concentration with the difference in the number of tissue layers that separate the maternal and fetal bloods in these two forms—one in the rabbit, five in the sheep—but further measurements of the physical characteristics of each placental type will be necessary before any conclusions can be drawn as to the particular feature or combination of features of the tissue barriers responsible for the difference in the concentration gradient. This point may be clarified by a consideration of the relationship of the several factors that modify the movement of oxygen from one plasma to another.

On the assumption that the tissue barrier separating the two blood streams in the placenta can be represented by a liquid layer or a liquid impregnated membrane the relationship of the factors may be expressed as:

$$\dot{Q} = \frac{\Delta C \cdot A \cdot K}{D}$$

where $\dot{Q}$ represents the millimols of gas transferred per unit time, ΔC the O_2 concentration gradient on the two surfaces of the liquid layer, A the area of the surface at right angles to which the diffusion takes place, D the distance between the two limiting surfaces of the liquid layer or its thickness and K a constant for the system. In terms of placental transfer of oxygen, $\dot{Q}$ represents the oxygen consumption of the fetus in millimols per unit time and would usually be expressed in cc. per minute. ΔC the single difference in plasma oxygen concentration that would effect the same net transfer as the changing values that occur as the bloods are exposed to each other in the placental capillaries (what we have referred to as the concentration

gradient), A is the area of the smallest surface interposed between the maternal and fetal plasmas, and D, the average distance between them. In short, the main factors that would affect the placental transfer of oxygen are:

(i) The concentration gradient, ΔC.

(ii) The limiting surface area A; a factor that becomes more obvious in its importance if we consider the possibility of a cone-shaped placenta. The surface of the fetal capillaries might represent the narrow end of the cone.

(iii) The thickness of the tissue across which transfer must occur.

(iv) Variations in the solubility of oxygen in the different tissue layers that form the placental barrier.

(v) Changes in K, the Fick diffusion coefficient across the membranes. The fact should be recognized that the concentration gradient itself represents a difference between two quantities, each of which is the result of a steady state, for it will be apparent that the average concentration of the oxygen in the fetal plasma of the placental capillaries will increase as the rate of blood flow through them and the umbilical vessels slows, other factors remaining the same. This rise in concentration would result in a decrease in the concentration gradient of the physically dissolved oxygen. Accordingly, the rates of uterine and umbilical blood flow are factors with effects on oxygen transfer that manifest themselves through alterations in the concentration gradient. Finally, the fact must be recognized that in any multilayered barrier the different layers may be acting as limiting factors for different reasons—one layer may present the smallest surface area and another a low solubility.

In the sheep, for example, an increase in the surface area, A, across which diffusion takes place would serve to increase the quantity transferred in unit time though the other factors, the concentration gradient C, D, the diffusion distance, and K remain unaltered. And some such change must occur as the oxygen requirements of the fetal lamb increase *in utero* with advancing age for the oxygen concentration gradient remains relatively stable during the last two-thirds of the gestation period. That the change may be one in surface area is suggested by the fact that the volume of blood in the fetal side of the placenta increases steadily until around 110 days' gestation age; thereafter as the volume of blood in the fetal placental vessels

the size of the fetal vascular bed—and the O_2 concentration gradient remain relatively unchanged, it would appear that the increasing demands of the fetus are met by changes in D, the intercapillary distance, or in K.

So, too, in the rabbit the small difference in the concentration of the physically dissolved oxygen, ΔC, on the two sides of the placenta may be associated with a small diffusion distance D, but it may as well be related to the presence of a large surface area across which diffusion may take place large, that is, relative to the oxygen requirements of the fetus.

The next step in this study of the placental exchange of the respiratory gases should be an estimation of the surface area, A, available for diffusion per unit weight of fetus in these different placental types.

SUMMARY

Oxygen dissociation curves were prepared with the fetal and maternal bloods of pregnant rabbits in the last week of gestation and used together with the degrees of saturation of the hemoglobin in the bloods from the four placental vessels—uterine artery, uterine vein, umbilical artery, umbilical vein—to estimate the oxygen concentration gradient across the placenta. The data indicate that the difference in the plasma oxygen concentration on the two sides of the placental barrier is *circa* 0.013 millimols per liter.

REFERENCES

1. Barcroft, J. and Barron, D. H.: Observations upon the form and relations of the maternal and fetal vessels in the placenta of the sheep. Anat. Rec., 1946, *94*, 569.
2. Barron, D. H.: Some aspects of the transfer of oxygen across the syndesmochorial placenta of the sheep. Yale J. Biol. Med., 1951, *24*, 169.
3. Barron, D. H. and Alexander, G.: Supplementary observations on the oxygen pressure gradient between the maternal and fetal bloods of sheep. Yale J. Biol. Med., 1952, *25*, 61.
4. Grosser, O.: *Frühentwicklung, Anatomie und Entwicklungsgeschichte des Uterus und des Placenta*. Vienna and Leipzig, 1909. 314 pp., six plates.
5. Mason, M. F.: A note on the manometric estimation of oxygen in small samples of blood. J. Physiol. (Lond.), 1939, *94*, 530.
6. Moessman, H. W.: The rabbit placenta and the problem of placental transmission. Amer. J. Anat., 1926, *37*, 433.
7. Rosenthal, T. B.: The effect of temperature on the pH of blood and plasma *in vitro*. J. biol. Chem., 1948, *173*, 25.

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CLASSIFICATION OF THE HUMAN SENSES

The recent edition of the *Textbook of physiology*, edited by Fulton, reveals the enormous strides made in this field during the past fifteen years.[1] Similar advances have been achieved in the increasingly closely related discipline of experimental psychology, a science that only a few decades ago was compartmentalized into artificial groups, such as Sensation, Cerebration and Intellection, and Tendency to Action (William James).

What has fundamentally changed the approach to problems in all areas of psychology is the concept of dynamic structure—a pattern of stress determined by the integration of divergent forces—as originally propounded by the gestalt psychologists Wertheimer, Kohler, Koffka, and their followers.

Replacing the atomistic viewpoint of previous authors, this concept has furnished the basis for such contributions as the Topological Field Theory (K. Lewin), the Sensory-Motor Synergy Theory (W. S. Boernstein) and Sensory-Tonic Theory (H. Werner), the Cybernetic Contribution to Perception (M. Wiener, W. Pitts, and W. S. McCulloch), and, most recently, the Theory of Event-Structure (Floyd Allport).

Indeed, the concept of structure plays a decisive rôle not only in the study of the personality as an articulated whole, but also of single senses—vision, audition, and touch. Yet when it comes to *classifying* the senses of man, to evaluating them according to one common principle, even gestalt psychologists have avoided the challenge, while other modern psychologists as well as physiologists still tend to fall back on the old blueprints of nineteen-century authors.

Historically, following Johannes Muller's anatomic physiologically oriented division of different parts of the nervous system according to specific sense energies, H. von Helmholtz arranged the pertinent psychological entities (sensations) according to "modalities." Cataloguing the modality of vision, the modality of audition, the modality of taste, etc., he made no attempt at evaluation but merely postulated that there were no transitions from any one modality to another.[2]

From a purely physiological standpoint, Charles S. Sherrington differentiated between "exteroceptors," responding to changes in the external

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environment, and "interoceptors," reacting to changes within the body. Again, the senses were graded not according to an over-all principle but, in this case, classified on topological grounds—the site of the receptive field. Also, as Ruch points out, clinical classification has been "strongly influenced by morphological considerations"[5] with no regard to the biological or psychological values of the senses.

From time to time, to be sure, there have been a few authors who have ascribed different values to the various senses, but their ideas were never developed beyond the initial stage of hypothesis. As early as 1904 the physiologist W. Nagel claimed that only "the so-called higher senses, vision and audition," are strictly separated from the other senses and from each other, but that transitions do exist between "the so-called low senses." However, he failed to explain what it is that determines the division into "high" and "low" senses.[6]

Perhaps the first author to view the human senses in their living context was Johannes von Kries, the foremost sense physiologist of his time. He classified the senses according to their capacities to convey precepts arranged in space. Vision and touch he designated as being the "spatial senses par excellence," while olfaction was placed at the other end of the scale, for it seemed doubtful to him that odors had any spatial order. Further, he spoke of "the sense of space" and "the sense of time" as being the products of several different factors, among them the voluntary movements. According to von Kries, these senses represent "a total of functions in which not only the single senses take part but manifold activities, particularly of the central nervous system."[7]

Here a basic property of man as a whole—his ability to experience space and time—was recognized as being the result of numerous activities integrated into one functioning pattern. Further, the capacity for spatial perception was used as the criterion for classifying the senses. Today, however, the question still remains as to whether this classification is justified and, if so, what are the morphological physiological differences underlying this psychological distinction?

Since the time of its publication a half century ago, von Kries' hypothesis has not been elaborated. Most students of sense physiology have been content to treat each sense separately, as if it were an entity isolated from the rest of the organism. Some authors have singled out one sense as being more important than all the others. Thus E. D. Adrian pointed out "the importance of the eyes to our cerebral activities and to our way of thinking." But G. Murphy emphasizes the "inner cues," suggesting that man "differs, indeed, from all other animals in being relatively free of direct dependence on immediate external stimulation."[8]

The foregoing brief historical review indicates the divergence in views up to the present. However, today's coalescence of physiology and psychology justifies the search for a principle for evaluating the senses which will apply equally to their psychological and somatic aspects. Here Gestalt Psychology, dealing as it does with the concept of structure in physical objects as well as in perceptual phenomena, supplies a key to the problem.

According to Wertheimer and Kohler, gestalten are "segregated wholes," structured by self-distribution and regulation of forces and material.[1] On the basis of physical data alone, Kohler had distinguished between "strong" and "weak" gestalten. This distinction will be elaborated and applied more generally in the following paragraphs.

In a strong gestalt, the configurating forces are well integrated and clearly determined in space. Thus the gestalt maintains itself as a stable, sharply delineated, dynamic pattern that resists pressures from without. It is a "positive" figure set off from the "negative" ground (E. Rubin).[2] It can be transposed in such a way that the relations within the gestalt remain unchanged. A strong gestalt is a dimensionally defined or spatial structure.

In a weak gestalt, the configurating forces offer little resistance to pressures from without. A weak gestalt is unstable, fluctuating in structure, and tends to blend with the ground. Therefore it cannot be fully extracted from its surroundings. A weak gestalt derives its meaning from the total figure-ground situation of the moment. Because of the vagueness of its spatial delineations, a weak gestalt may be called "pre-spatial."

There are many gradations of strong and weak gestalten. The more highly differentiated a gestalt, the stronger must be its coherent forces. In other words, a high degree of spatial differentiation indicates great strength of the configurating forces.

When it comes to perceptual gestalten, however, one must take into consideration their physio-psychological nature. Gestalt Psychology, having originated in classical physics, treats perceptual gestalten as if they were isolated physical entities, claiming that "the forms of experience" are identical in structure with the underlying physical gestalten in the nervous system.

Actually, a perceptual gestalt depends largely on the over-all level of organization of the perceiving system. Of necessity, the concept of "levels" of perception" is alien to Gestalt Psychology, as is therefore the idea of classifying the human senses. Indeed, it is not by chance that this school has dealt only with the high senses, ignoring taste and smell.

In a physical gestalt, the configurating forces are inherent and self-distributing; those in a perceptual gestalt are not. A perceptual gestalt (a heard melody, a viewed painting) is part of a larger whole—the perceiving

individual. The configurating forces arise outside the pertinent sensory sector of the brain and are supplied, as this writer has indicated elsewhere, by the individual's basic tonus apparatus and its specialized branches. Perceptions are the result of either massive or specialized "sensorimotor synergies"; in other words, "perceptions are acts."[2,3] Each perception is both impression and expression of the individual.

The integration of sensory and motor processes in perception has been demonstrated by this writer in experiments on frogs and toads, monkeys (where gustatory acuity depended on intactness of the sensory as well as motor cortical areas), and on brain-injured and normal human beings.[4] That perceptual processes are intimately bound up with the given personality was shown in other experiments this writer conducted together with W. Jaensch at the University of Berlin years ago. Contrary to the classical gestalt concept, our findings at the time revealed that the kind of perceptual response was dependent upon the particular psychosomatic type of the subject.[5]

Strong perceptual gestalten appear relatively late in phylo- and ontogenesis, marking a turning point in mental development. Indeed, it is only the strong perceptual gestalten, with their transposable intrinsic meanings, constancy and tendency to pregnance—hence largely independent of the momentary constellation—that provide the basis for objectivity, abstract thinking, and artistic creation.

Generally speaking, normal perception is predicated upon two conditions: first, the available physical objects, regardless of whether or not they are gestalten in themselves; secondly, that mechanism within the individual which is capable of translating the qualities and spatial order of those objects into a perceptual gestalt.

In other words, the level of a perceptual gestalt is partly conditioned by the spatial order of the external objects. The more complex the spatial relations of a given stimulus constellation, the stronger and more highly differentiated is the resultant perceptual gestalt—provided the underlying sensorimotor mechanism is more highly differentiated. Those senses that are structured in such a way as to be capable of strong perceptual gestalten may be classified as the *high or spatial senses*, while those senses that can convey only weak gestalten are the *low or pre-spatial senses*.

The problem of why some senses in the adult human being have not matured, while others have reached a high stage of development, extends beyond the confines of Gestalt Psychology. It is elementary that each sense is "tuned" to its own external agents, with the sense of smell responding to odors and not, for instance, to light waves, the auditory sense to sounds and

not to tastes, etc. Yet it is not the qualities of these agents that determine the level of organization of a sense, but their spatial relations.

Vision, for example, is not a high sense because it responds to colors, but rather because it is organized in such a way as to be capable of cognition of the highly differentiated patterns available in the visual field. The corresponding is true for the tactile sense, and also for audition where "quasi-spatial" structures are provided by the frequencies of acoustic waves.

Only by regarding a sense as a plastic sensorimotor organization can one understand why the spatial order of external objects has such a decided influence upon the level of development of a sense. Indeed, far from being "a segregated whole," a sense, like any biological system, is open to the outer world and can only exist by continually receiving energies and material from its environment (food and adequate stimuli), assimilating them, and giving off products of its own. Consequently, the morphological-functional structure of a sense is the product of continual fusion of its inherent energies and material with those of its environment.

The formative role of the environment in regard to the whole organism has been stressed by S. Hecht: ". . . the environment adapts the organism to itself." This statement is equally valid for any living part, including the senses. In addition to the environment shared by all the organs of the body, each sense has its own special external environment in the form of adequate sensory stimuli. Thus stimuli in the form of light waves for vision, of acoustic waves for audition, etc., not only influence the substance of the sensory system, but help to shape its sensorimotor organization, by excitation and inhibition.

Where the outer environment is structurally primitive, as with physical odors, warmth or cold, the sense cannot mature beyond the low level of these weak gestalten. Only where the external environment is well articulated, as with optic, acoustic, and tactile objects, can the sense reach a high level of development.

In the course of evolution, perception starts with weak gestalten in all the senses. Gradually, along with the emergence of more specialized structures in the nervous system, more and more differentiated and integrated perceptual gestalten become possible in the high senses. They, however, retain their low sensory functions as well. For instance, perception of light and dark in vision and noises in audition are low sensory functions of high senses. Both high and low sensory functions are vital to the human being, with the high sensory functions serving his cognition of the outer world and the low ones largely his autonomic needs.

A low sense is characterized anatomically by a poorly organized sensorimotor system with a relatively diffuse reception area in the cerebral cortex.

and a close connection with the autonomic nervous system (hypothalamus). Physiologically, a low sense can give rise only to weak configurating forces which are helpful in maintaining the internal environment. Psychologically a low sense can develop only weak perceptual gestalten, not clearly separated from emotion.

Olfaction and taste are among the low senses. Taste, however, being closely related to the tactile sense, does have a synapsis in the thalamus opticus.[6] It is also closely connected with the digestive system and plays an important rôle in nutrition. The ability to locate gustatory stimuli is rather poor, as is its cognitive capacity.

Olfaction, being largely concerned with visceromotor activity, is on an even lower level of development than taste. The sense of smell is represented in the most ancient part of the human brain and its connection with the thalamus, if any, is extremely tenuous, its sensorimotor apparatus poor. Hence there is no ability to perceive highly differentiated (spatial) gestalten.[7] Actually, the location of odors can only be gauged by their intensity.[8]

In accordance with the definition of weak gestalten, olfactory precepts are unstable, with little objective value, open to suggestion, and part and parcel of the total situation of the moment. Odors derive their meaning for the individual chiefly from a particular situation or activity in which they once played a rôle.

Thus, in tests conducted by this writer, odors were described by children as well as adults in "concrete" terms, such as: "like a rose," "it has something to do with a pharmacy," "like the soap we use at home," etc. Clearly, in olfaction, personal affective experience outweighs the cognitive response.

A high sense is characterized anatomically by a well-structured sensory system with a relay station in the thalamus opticus (for perceiving space and time), a sharply defined cortical reception area, and a highly differentiated specific tonus apparatus which supplies the dynamics for the pertinent strong perceptual gestalten. Physiologically, it has the ability to generate strong as well as weak configurating forces. Psychologically, it is able to develop strong as well as weak perceptual gestalten. Pathologically, agnosia is possible only in the realm of high senses. The senses conforming to this description are vision, audition, and touch (which is a composite of several subsidiary functions).

Of all the senses, vision plays the most important rôle in man's orientation. Moreover, vivid optic activity has been found by this writer to occur even in total darkness ("induced hallucinations") in response to nonadequate stimuli that increase the body tonus, such as the taste of sugar, ultraviolet rays on the skin, or abrupt muscle contraction.[9]

Audition, by making speech and music possible, contributes immeasurably to the interhuman relationship. The tactile sense, of course, supplies strong perceptual gestalten of its own. Particularly striking is the integration of tactile sensation and movement.

It is through man's high senses that he is able to perceive the world in terms of space and time. For this level of perception, the individual's frame of reference is supplied by the specialized branches of his tonus apparatus. Since all human beings are equipped with the motorium guaranteeing space-time perception, they are all capable of strong perceptual gestalten.

In this way the high senses make possible the sharing of perceptual gestalten with other individuals. It is this common experience of transposable gestalten that provides the means for thinking, and leads to communication of ideas. Thus it may be said that the ability of the high senses to perceive spatial relations is the fountainhead of cultural progress.

To sum up, different senses in the adult human being are on different levels of organization. These differences depend partly on internal factors in the individual, partly on the formative influence exerted by the spatial arrangement of the external objects to which the particular sense is attuned. Only highly organized sensory systems can convey perception of well-differentiated objects; only well-differentiated objects can provoke the development of highly organized sensory systems.

The high senses of vision, audition, and touch are the spatial senses; the low senses, such as taste and olfaction, are pre-spatial. Thus the senses may be classified anatomically, physiologically, and psychologically according to their capacity for spatial perception.

This writer is indebted to Professors K. S. Lashley and George Gaylord Simpson for their constructive criticism in formulating this paper, and to Henrietta Gilden for the editing.

REFERENCES

1. Adrain, E. D.: *The physical background of perception.* Oxford, Clarendon Press, 1946, p. 54.

2. Boernstein, W. S.: On the sense of smell. (title trans.) Dtsch. Z. Nervenheilk., 1928, *101*, 55-91, 173-207.

3. Boernstein, W. S.: *Der Aufbau der Funktionen in der Hosphare.* (The functional structure in the auditory cortex.) Berlin, S. Karger, 1930.

4. Boernstein, W. S.: On the hormonal regulation of the correlation between sensory functions and body tonus. (title trans.) Klin. Wschr., 1931, *28*. Also: On the interrelation of sensory systems: psychological experiments. (title trans.) Ned. Tijdschr. Psychol., 1933, *1*, 331-334. Also: On the functional relations of the sense organs to one another and to the organism as a whole. J. Gen. Psychol., 1936, *15*, 117-131.

5. Boernstein, W. S.: On the physiological basis of perception: the influence of "bright-dark" stimuli on the state of melanophores in amphibians. (title trans.) Arch. int. Pharmacodyn., 1939, *61*, 387-417.

6. Boernstein, W. S.: The cortical taste area in monkeys and a semi-quantitative method of testing taste in monkeys. Amer. J. Physiol., 1940, *129*, P314.
7. Boernstein, W. S.: On the physiologic basis of hallucinations and dreams. Proceedings of the Rudolf Virchow Medical Society, Vol. 9, 1950. Also: On the physiological basis of hallucinations, including dreams. Proceedings and papers of the Thirteenth International Congress of Psychology, Stockholm, 1951.
8. Fulton, John F., Ed.: *A textbook of physiology*. 17th ed. Philadelphia, W. B. Saunders Co., 1955.
9. Hecht, S.: Quoted by Murphy, G. in *Personality*. New York, Harper & Bros., 1947.
10. Helmholtz, H. von: Die Tatsachen in der Wahrnehmung. In: *Schriften zur Erkenntnistheorie*. Paul Hertz and M. Schlick, Eds. Berlin, Julius Springer, 1921.
11. Kohler, W.: *Die physischen Gestalten in Ruhe und im stationaren Zustand*. Brunswick, F. Vieweg und Sohn, 1920. Also: *Gestalt psychology*. New York, Liveright Publishing Co., 1947.
12. Kries, J. von: Zur Psychologie der Sinne. In: *Handbuch der Physiologie des Menschen*, Vol. III. Brunswick, F. Vieweg und Sohn, 1904, p. 18.
13. Murphy, G.: *Personality: A biosocial approach to origins and structure*. New York, Harper & Bros., 1947, p. 262.
14. Nagel, W.: Allgemeine Einleitung zur Physiologie der Sinne. In: *Handbuch der Physiologie des Menschen*, Vol. III. Brunswick, F. Vieweg und Sohn, 1904.
15. Ruch, T. C.: Somatic sensation. Chapter XVIII in: *A textbook of physiology*. J. F. Fulton, Ed. 17th ed. Philadelphia, W. B. Saunders Co., 1955.
16. Ruch, T. C., Blum, M., and Brobeck, J.: Taste disturbances from thalamic lesions in monkeys. Amer. J. Physiol., 1941, *133*, 433-434. Also, Blum, M., Walker, A. E., and Ruch, T. C.: Localization of taste in the thalamus of Macaca mulatta. Yale J. Biol. Med., 1943, *16*, 175-191. Also, Patton, H. D., Ruch, T. C., and Walker, A. E.: Experimental hypogeusia from Horsley Clarke lesions of the thalamus in Macaca mulatta. J. Neurophysiol., 1944, *7*, 171-184.
17. Sherrington, C. S.: *The integrative action of the nervous system*. (Silliman Memorial Lectures.) London, Constable Co., 1906.
18. Skramlik, E. von: *Handbuch der Physiologie der niederen Sinne*. Leipzig, J. Thieme, 1926.

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STEREOTAXIC IMPLANTATION OF CALIBRATED Pd^{109} AND Y^{90} SPHERES: A TECHNIQUE FOR PRODUCING PREDICTABLE SUBCORTICAL LESIONS IN THE BRAINS OF LABORATORY ANIMALS‡§

When Horsley and Clarke[6] introduced their stereotaxic manipulator in 1908, all subcortical areas in the brains of laboratory animals theoretically became accessible for study. As a consequence, many valuable data have been obtained from stimulation and ablation studies. The potential of the technique for ablation study has been limited for want of a necrotizing agent that would gradually destroy a predictable volume of tissue. In 1952, Carpenter and Whittier[4] reviewed the work of others and demonstrated that stereotaxically implanted radon seeds create a more discrete lesion than any of the chemical, electrolytic, mechanical, or thermal methods.

Others had explored the possibility of utilizing radium emanations, but never perfected it as an adjunct for stereotaxic surgery. Edwards and Bagg,[5] in 1923, were probably the first to demonstrate that subcortically placed radon caused localized destruction with minimal disturbance of contiguous and overlying structures. They used a free-hand applicator for placement. Stein and Peterson,[11] after stereotaxic implantation of a radon seed in the mesencephalon of a rhesus monkey, suggested in 1950 that this methodology might prove to be a useful adjunct to neurophysiological research and, eventually, to clinical neurosurgery. In 1951, Borison and Wang[1] destroyed the vomiting center of the dog by free-hand placement of radon seeds in the medulla oblongata. Their study was the first to demonstrate a correlation between radiation strength and lesion size in the central nervous system. These authors also pointed out that the gradual development of necrosis resulting from the radiation effect had a distinct advantage

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§ This technique could not have been developed without the constant advice and technical assistance rendered by colleagues, too numerous to name individually, who are members of the staff of the Radiological Research Laboratory at the College of Physicians and Surgeons.

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when experimentation involved a sensitive area. Cairns and Fulton[1] in 1930 were the first deliberately to utilize this characteristic of radon, when studying the effect of gradual destruction of the spinal cord.

Encouraged by the findings of others, experimentation was undertaken with stereotaxically implanted radon seeds, only to be abandoned because of several inherent disadvantages. Bulk proved to be a distinct hinderance when multiple placements were required, and the necessity of having to work with a certain percentage of gamma radiation was another.

MATERIALS AND METHODS

Work was then undertaken with artificially produced radioactive isotopes which were sources of beta rays. Employment of these substances assured a reduction in volume of the implant and provided the additional advantage in selection of half life, as well as maximum energy of the beta particles emitted.

Palladium-109 and Yttrium-90, pure sources of beta radiation, were tested at this point. Pd^{109} has a relatively short half life, 13.1 hours, in contrast to that of Y^{90}, 2.54 days. The maximum energy of the beta particles of the former is 0.95 mev compared with 2.18 mev for the latter. In the case of both isotopes, radiation strength drops off rapidly enough to permit permanent placement of solid spheres of either isotope. This geometric form was selected for ease of handling in apparatus, as was a diameter of 0.86 mm., because it permits free passage through thin walled, #18, steel tubing. Spheres were implanted under aseptic conditions with full anesthesia, intravenous Nembutal, 20 to 30 mg./kg. of body weight. The needle which carried the sphere to the calculated site in the brain was clamped to the electrode carrier of a stereotaxic manipulator. (It is a diminutive adaptation of a clinical radon applicator and is operated as such.) A fuller description and the details of operation of this and other apparatus used in the technique are available in another communication.[2] It may be appropriate at this point to state that the exposure of the operating personnel is well below the permissible limit, based on repeated monitoring.

Pd^{109}, when inert, is the noble metal palladium. Solid spheres with a uniform diameter are easily made in the laboratory by fusing accurately measured lengths of palladium wire in a ceramic crucible by means of an illuminating gas-oxygen flame. Yttrium, a rare earth, is maintained in a solid beta quartz sphere (Fig. 1), which prevents leaching of the yttrium, and causes a negligible tissue reaction when inert. This geometrical form and physical state are obtained by a process described by Gmelin[3] and Doering.[4] In brief, this consists of fusing a mixture of a ceramic clay, montmorillonite, and Y_2O_3, 50% by weight, at a temperature of 1440° C. Mont-

* The authors are particularly grateful for the personal effort of Dr. William S. Gmelin of the Brookhaven National Laboratory in developing the technique for fabricating the Y^{90} spheres, and to Mr. Louis Stang, Head of the Hot Laboratory Operations Division, Brookhaven National Laboratory, for having made time and facilities available for this portion of the project.

morillonite is composed of chemical elements with such short half lives that Y^{90} remains the only effective radioactive constituent an hour after removal of a sphere from the reactor. Prior to activation in the reactor, all spheres are tested for size and weight, and then run through the apparatus employed in sorting, calibrating, and implanting them when radioactive. This is done to prevent jamming.

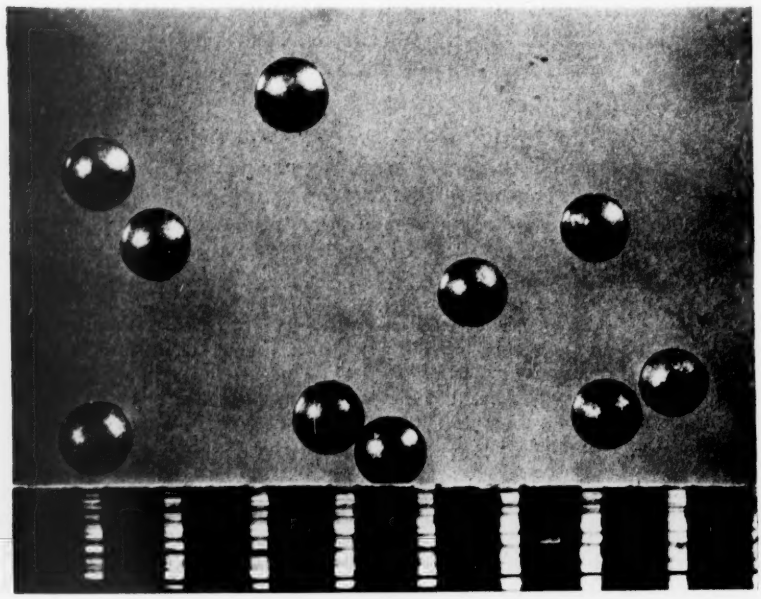

FIG. 1. Photographic enlargement of a group of ceramic spheres containing yttrium. (Reprinted by courtesy of the Atomic Energy Commission, from the Brookhaven National Laboratory Bulletin 341 [T-60], 1955.)

LESIONS

The lesions which result from implantation of the sources of beta radiation described above are spherical and discrete by gross examination (Figs. 2 and 3). A 400 to 700 μ zone of irregular transition from necrotic to normal cells surrounds the area of absolute destruction. Histological study of this perimeter shows the astrocytes are most sensitive to radiation, next the microglia, then the neurons, and oligodendroglia. The blood vessels and myelin are the most resistant. The irregularity of transition is manifested by the presence of normal appearing neurons, myelin sheathes, and capillaries within 10 μ of the area of liquefied cellular breakdown, while fragmented neurons are found 600 to 700 μ out from this point. Gitter cells are

plentiful in the liquefied area of destruction, but not in the transition zone. Polymorphonuclear leucocytes are not seen in any portion of the lesion after the first five days, but are seen in the needle tract until healed. No explanation of this schedule is readily available, nor for the unpredictably normal

FIG. 2. H and E photographic enlargement showing extent of radionecrosis 15 days after stereotaxic implantation of Y^{90} source, approximately 0.5 mc. in strength, in telne septum pellucidum. Empty space in septum was the site of implant.

appearance of certain neurons, myelin sheathes, and capillaries in zones where the majority are necrotic or moribund. These findings were obtained from a study of single lesions made in the head of the caudate nucleus, the opposite side serving as a control. Variation of the radiation strength of the sources implanted in this area, as well as the time of sacrifice, provided data concerning volume of tissue destroyed by known amounts of radiation and also showed the gradual necrotizing effect of beta radiation.

Micrometry after histological preparation was employed at first in determining lesion volume. This method was discontinued because of difficulty in accounting for shrinkage. Supravital staining and photographic recording

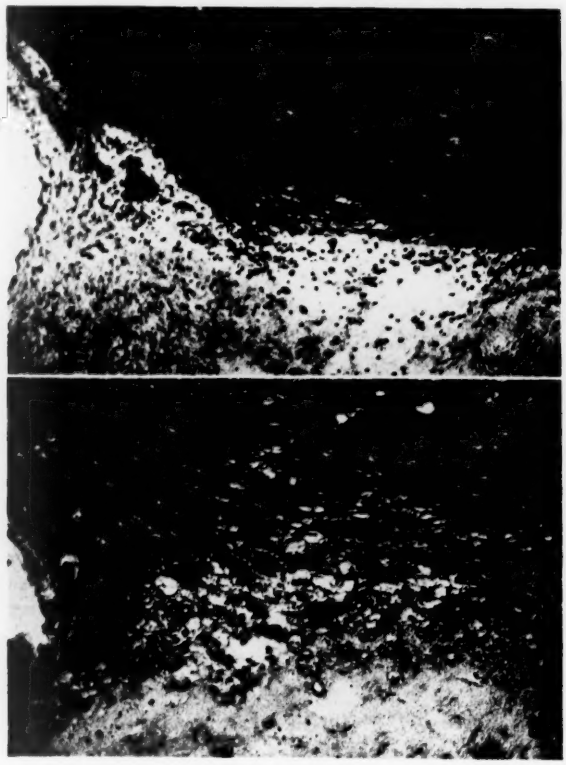

FIG. 3A. Mahon stain, x220. Photomicrograph to show abrupt line between normal and abnormal myelin in the corpus callosum in the superior left portion of the lesion illustrated in Figure 2.

B. H and E stain, x220. Photomicrograph to show in greater detail the changes in the upper left margin of the lesion illustrated in Figure 2.

proved to be more reliable methods for determining gross lesion diameter. This was accomplished by administering 5 ml. of 4% Evans blue dye (W761-1)* by the intravenous route three hours prior to sacrifice. Dis-

* This chemical was generously made available by Warner Lambert Pharmaceutical Company, 113 West 18th Street, New York City.

tortion of the brain was minimized by perfusing the vascular system via the left cardiac ventricle with 300 ml. of a solution containing 10% formalin, 0.9% sodium chloride, and 5.6% gum acacia under a pressure of 120 mm. of mercury." Both procedures were carried out under full intravenous Nembutal anesthesia. In addition to outlining the area of absolute necrosis, supravital staining revealed a surrounding area where the integrity of the blood brain barrier is temporarily interrupted. The transition from absolute necrosis to minimal change was well revealed by this method. The degree of staining by the dye diminished with distance from the source. Changes in the astrocytes corroborated this gross colorimetric determination.

The most important factors that determine lesion volume are: source strength, energy of the beta ray, half life, and self-absorption of radiation within the source. The maximum diameter of tissue destruction will ultimately depend upon the energy of the particular beta ray employed. However, within these limits the volume of the lesion can be adjusted by varying the strength of the source. Since each type of cell has a level of resistance to radiation, the lesion will increase according to the dose rate. This, in turn, is dependent upon the strength of the source and its half life. Self-absorption of radiation within the source is definitely a factor. The low specific gravity of the ceramic matrix of the Y^{90} spheres raises the efficiency of delivery of the total dose, whereas in the more dense metallic Pd^{109} sphere, much of the total beta radiation is restrained within the source.

Data obtained from research with solid Pd^{109} spheres of approximately identical radiation strength illustrate (Fig. 4A, B, and C) the gradual development of the lesion to its maximum diameter on the fourth day, and its status in the fourth week (Fig. 4D), when peripheral edema has subsided and healing and repair are evident. The first three pictures can be easily reconciled as recording the effect of increasing numbers of millicurie hours of radiation. These photographs indicate that no reliable correlation can be made between an anatomical deficit created by this method and resultant physiological changes until the third postoperative week, because of edema within the area of absolute necrosis and its immediate periphery. However, this method of tissue destruction has a distinct advantage over others in that the lesion develops slowly. In this way the organism can withstand a greater assault.

EVALUATION OF THE METHOD

When calibration of the radionecrotic potential of various doses of the beta emitting isotopes, Pd^{109} and Y^{90}, was complete, the efficacy of the method was tested by stereotaxic implantation of both types of sources in

various subcortical centers. These were the following: head of the caudate nucleus; septum pellucidum; "preoptic region" as defined by Heath,[7] viz., "rostrally from the region of the anterior commissure about 5 mm. and laterally into the ventromedian aspect of the caudate nucleus"; and the last

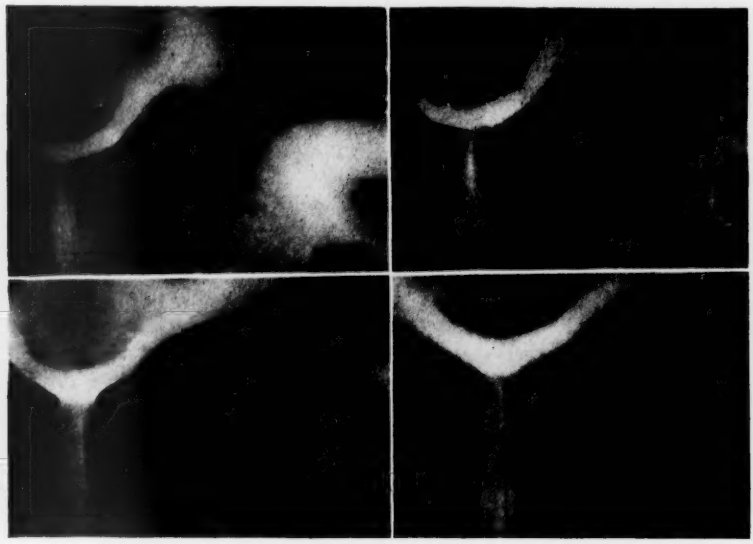

FIG. 4. Supravital stain, Evans blue dye (W761-1). Photographs of identical magnification, showing the status of lesions in the caudate nuclei of cats at different intervals after implantation of Pd^{109} spheres of approximate radiation strength. Sacrifice time: A, 11 hours; B, 24 hours; C, 4 days, at which time the lesion has reached a maximum diameter which is maintained for approximately 10 days; D, 24 days. Note the reduction in deposition of the dye peripheral to the lesion and enlargement of the ventricle which is compensatory for resultant tissue loss in the caudate nucleus. (By permission of the publisher of the Journal of Comparative Neurology, from Ref. 2, in press.)

two areas in combination. Animals survived these lesions satisfactorily, unless the swelling was of sufficient degree to occlude the foramina of Munro and cause an overwhelming increase of intracranial pressure. A post-mortem verification of this was marked ventricular enlargement caudal to the area of edema. Eight animals in a series of forty three succumbed from this cause. Death under these circumstances occurred on the third to sixth day, when the lesion was reaching its maximum dimension. The significance of minor changes in the serum sodium and potassium levels coincident with these lesions is discussed in another communication.[10] It is per-

tinent, however, to mention that when over 50% of the volume of both caudate nuclei was destroyed, the only deviation from the physiological norm was anorexia to a degree necessitating gavage for the first four post-

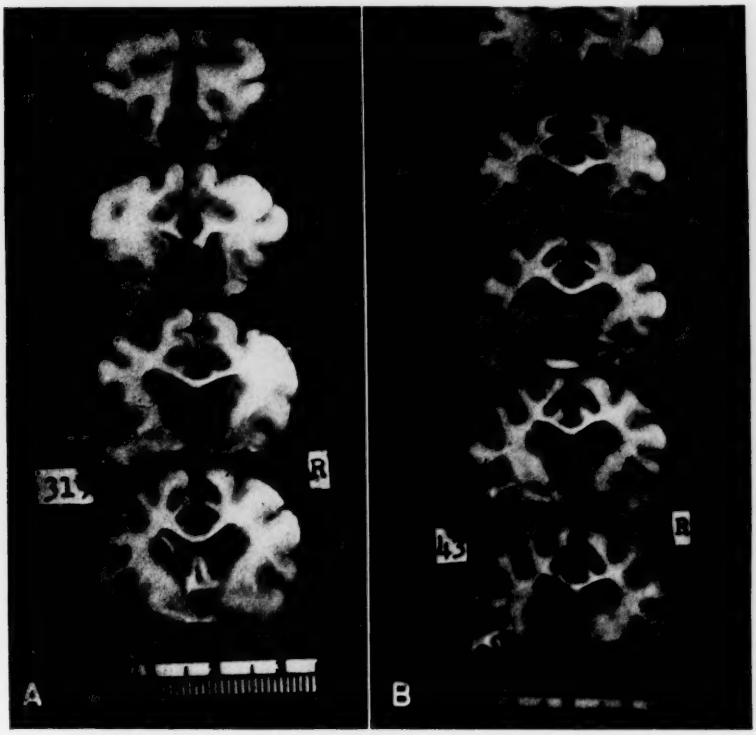

FIG. 5. Supravital stain, as above. Photographs of lesions caused by implantation of one Y^{90} sphere, approximately 0.4 mc. in strength, in the septum pellucidum. A, and in the middle of the area specified by Heath, B. Sacrificed on the 22d day and 21st day post implant, respectively. (By permission of the publisher of the Journal of Comparative Neurology, from Ref. 2, in press.)

operative weeks. From then until sacrifice in the sixth week, the animals ate satisfactorily. A lesion involving the preoptic area as defined by Heath (Fig. 5A), or one which included the septum pellucidum, anterior commissure, and descending portion of the fornix, as illustrated in Figure 5B, did not cause a detectable neurological or behavioral change. These lesions, with an approximate diameter of 7.5 mm., resulted from single Y^{90} sources

with an approximate strength of 0.4 mc. each. It is of interest that these particular animals and others with similar lesions did not show the loss of affect, hypokinesia, and other profound disturbances reported by Heath. Possibly the discrete character of the lesion and its gradual development accounts for the difference.

CONCLUSION

It is to be concluded that Pd^{109} and Y^{90}, when employed in the method described above, are useful sources of beta radiation for the creation of quantitated, histologically standardized subcortical lesions. Y^{90}, which emits a stronger type of beta radiation and has a longer half life, appears to be the isotope of choice for stereotaxic neurosurgery. These characteristics make it particularly useful because it can be shipped to laboratories situated at a distance from an atomic pile without great loss of radiation strength. These laboratory data have been sufficiently convincing to permit preparation for clinical employment of the technique.

REFERENCES

1. Borison, H. L. and Wang, S. C.: Quantitative effects of radon implanted in the medulla oblongata: A technique for producing discrete lesions. J. comp. Neurol., 1951, *94*, 33-56.
2. Boyesen, S. and Campbell, J. B.: Stereotaxic implantation of artificially produced radioactive isotopes: A technic for producing quantitated subcortical lesions in the brains of laboratory animals. J. comp. Neurol. (Accepted for publication, 1955).
3. Cairns, H. and Fulton, J. F.: Experimental observations on the action of radon on the spinal cord. Lancet, 1930, *2*, 16-18.
4. Carpenter, M. B. and Whittier, J. R.: Study of methods for producing experimental lesions of the central nervous system with special reference to stereotaxic technique. J. comp. Neurol., 1952, *97*, 73-132.
5. Edwards, D. J. and Bagg, H. J.: Lesions of the corpus striatum by radium emanation and the accompanying structural and functional changes. Amer. J. Physiol., 1923, *65*, 162-173.
6. Ginell, W. S. and Doering, R.: Preparation of fused clay radiation sources. I. Yttrium macrospheres. Brookhaven National Laboratory Bulletin 341 (CT-60), 1955, 1-5.
7. Heath, R. G., Weber, J. J., Hogan, C., and Price, T. D.: *Studies in schizophrenia*. Ed. by R. G. Heath. Cambridge, Harvard University Press, 1954, Section II, Chap. 2, pp. 61-81.
8. Horsley, V. and Clarke, R. H.: The structure and functions of the cerebellum examined by a new method. Brain, 1908, *31*, 45-124.
9. Koenig, H., Groat, R. A., and Windle, W. F.: A physiological approach to perfusion fixation of tissue with formalin. *Stain Tech.*, 1945, *20*, 13-22.
10. Reilly, J. A., Hoyde, C. A., Du Pree, A. L., Boyesen, S., Campbell, J. B., and Mettler, F. A.: Serum sodium following experimental lesions in the feline brain. (To be published.)
11. Stein, S. N. and Peterson, E. W.: The use of radon seeds to produce deep cerebral lesions. Proc. Soc. exp. Biol., 1950, *74*, 583-585.

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ACTIVITY OF KNEE JOINT PROPRIOCEPTORS RECORDED FROM THE POSTERIOR ARTICULAR NERVE†

In recent years it has become possible for the first time to support the term "joint sense" with scientific evidence which proves that such a mechanism actually does exist. In 1944 Gardner[6] presented a thorough investigation of the innervation of the knee joint in cats and described the various types of sensory endings which are found in the capsule. He concluded that the Ruffini type endings appear to be derived from the posterior and medial articular nerves which are branches of the tibial and femoral nerves respectively. Andrew and Dodt[2] recorded firing from the medial articular nerve in response to joint movement, and others[3, 4, 7] have reported firing from the posterior articular nerve of the cat in response to knee joint movements. The chief difference between the activity of medial nerve proprioceptors[2] as compared with posterior nerve proprioceptors[4] was that the former seemed uniformly to be slow adapting type receptors which fired only during critical joint angles, while the latter appeared to fall into a fast adapting type, which fired only during joint movement, and a slow adapting type, which usually fired at most angles measured. This difference may conceivably have been the result of the restrictions imposed by the experimental method of Boyd and Roberts,[3] since it is apparent that they could only move the joint through roughly one-third of its normal range.

The purpose of the investigation described below was to determine the activity of posterior nerve proprioceptors during the full physiological range of flexion-extension movements.

METHOD

Cats were decerebrated by a mid-collicular lesion. An incision was made in the posterior surface of one of the hind limbs, usually the left, and the popliteal fat pad was removed. The heads of the gastrocnemius were separated to expose the tibial

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nerve. The tibial nerve was sectioned and dissected free in the direction of the popliteal fossa until the posterior articular branch was identified. The posterior articular nerve was cleared of fascia for a length of approximately 3 cm. Special electrodes which have been previously described[5] were placed upon the articular nerve and the wound was closed.

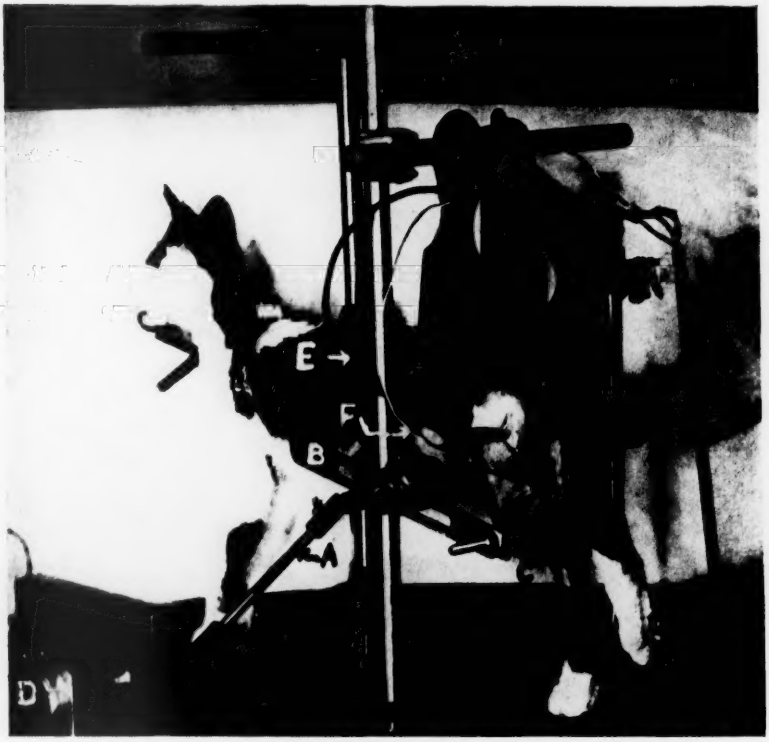

FIG. 1. Experimental arrangement. A—drive shaft; B—rotating blade; C—rod attaching rotating blade to leg of cat; D—potentiometer attached to drive shaft; E—ground wire; F—wires from *in vivo* electrodes.

A few experiments were also done in which the tibial nerve was sectioned above the point where the posterior articular nerve branches, thus producing an isolated articular nerve connected only to its sensory receptors in the capsule of the knee joint.

The animal was strapped in a rigid frame so that it was in a normal upright posture with its four feet just touching the table (Fig. 1). In a few of the original experiments, bone drills were placed in both heads of the femur and were then clamped to the rigid frame to immobilize the femur. This was subsequently found to be unnecessary since

the method of strapping the animal to the frame was sufficient to hold the femur immobile.

The joint rotating device consisted of a television antenna rotor* plus a series of shafts and gears (Fig. 1). When the shaft rotated, the animal's leg was moved and a corresponding rotation within the knee joint resulted. Any desired amount of rotation was produced by remote control with the rotor control box. The rate of joint rotation was varied by changing gears. The final drive shaft was also connected to a potentiometer (Fig. 1, D) which was in turn connected to channel B of a dual beam oscilloscope to obtain a record of joint position and movement.

The recording electrodes from the posterior articular nerve were connected to preamplifiers which led to channel A of the oscilloscope. Records of articular nerve firing at any given joint angle or during any given joint movement were viewed on the CRT and permanent records were made with a moving film camera.

Occasionally procaine hydrochloride was applied to the posterior articular nerve between the joint capsule and the recording electrodes to reduce the number of active receptor fibers and thus to enhance the possibility of obtaining single receptor records. It was frequently unnecessary, however, to use procaine since single receptors could easily be picked out of the record obtained from the intact posterior articular nerve.

At the completion of an experiment the posterior articular nerve was either sectioned between the knee joint and the recording electrodes or this region was soaked with 1% procaine. The joint was then moved through its full range as a control experiment to see if all firing in response to joint movement was abolished.

RESULTS

Joint movements were started from a position of maximum physiological extension and proceeded, by progressively flexing the leg against the thigh, to a position of maximum flexion. In the ten cats which were investigated not only did firing appear at the intermediate joint positions as has already been reported,[2-4] but firing also occurred beyond both ends of the intermediate range. In fact, proprioceptive activity was oftentimes most intense at the extremes of the flexion-extension range of the knee joint, as measured by both the number of active proprioceptors and the rate at which they were firing.

All angles of the knee joint were effective in eliciting firing from at least some of the proprioceptors. When total absence of firing was occasionally encountered in a preparation at certain angles, firing was subsequently induced at those angles by strongly stimulating the receptors with a series of repeated rapid movements of the joint, or by shifting the position of the recording electrodes. There is no angle of the knee joint, therefore, which is totally incapable of stimulating any of the proprioceptors.

An analysis of the firing pattern of single joint proprioceptors demonstrated that the typical receptor fired only during a specific range of joint

* Alliance Tenna Rotor, Model T-10

movement (Fig. 2). Each receptor responded to a different range of joint movements and, although there was considerable overlap in some of the ranges, no two receptors responded exactly alike. It is not possible to arrive at a figure to represent the average amount of joint movement during which a receptor fired because there was too much individual variation. One of the receptors recorded, for example, was active only during a range of 3° of joint movement, while another receptor in the same preparation fired during a range of 6.5°.

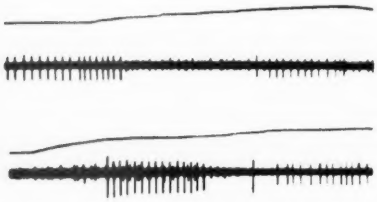

FIG. 2. Firing of different proprioceptors as the knee is rotated from a position of 70 degrees (lower photograph) to maximum flexion at 30 degrees (upper photograph).

The angle at which a receptor started to respond and the angle at which it ceased were usually very precise and consistent. The exact angle at which a receptor started to fire and that at which it stopped also depended on the direction of the movement. Figure 3 shows a receptor whose threshold at one end of its sensitivity range was investigated. The threshold angle was repeatedly 54.5° during a flexion movement but it was 56° during an extension movement. This was typical of all receptors studied.

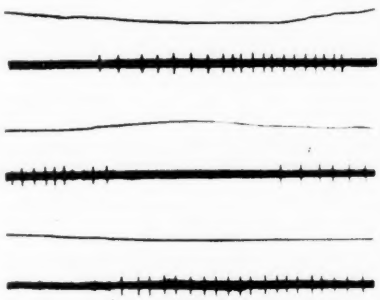

FIG. 3. Determination of the knee angle which is threshold for a given proprioceptor. The threshold which was investigated was at the flexion end of the activity range of the proprioceptor. Upper photograph—receptor starts firing at a joint angle of 56 degrees during an extension movement and ceases firing at 54.5 degrees as the leg is flexed again. Middle photograph—receptor stops firing at 54.5 degrees during flexion and starts again at 56 degrees during extension. Lower photograph—receptor starts firing at 56 degrees during extension. The threshold values are very consistent and the flexion and extension thresholds are always different.

Once a receptor started to fire during a joint movement its frequency increased as the movement continued until a maximum for the prevailing conditions was reached, after which the rate decreased until it ceased entirely as the joint was moved beyond the sensitivity of the receptor (Fig. 4). From such evidence it was quite clear that the typical receptor not only had a sensitivity range for joint movement but it also had a point of maximum sensitivity within this range.

The rate at which a receptor fires is determined by other factors besides

the particular angle of the knee joint. A fast rate of movement produced a generally higher rate of firing than a slow movement, and joint movement was usually a more effective stimulus than joint stasis (originally reported by Boyd and Roberts[1]).

FIG. 4. Response of a knee joint proprioceptor throughout its activity range. Lower photograph as extension proceeds the receptor is activated, its frequency increases and then in the upper photograph the firing rate decreases until its ceases entirely.

The amount of receptor adaptation depended greatly upon the angle at which the joint was immobilized. If the joint movement was stopped just beyond the angle at which a receptor started to fire, adaptation was more pronounced and sometimes the receptor would stop firing entirely. If a joint was stopped at an angle which was near the maximum sensitivity angle for a receptor, that receptor showed little adaptation. The joint proprioceptors were generally characterized by slow adaptation. At no time in any of these investigations was a receptor discovered which could be classified as a special fast adapting type receptor, always adapting quickly to zero when the joint movement ceased.

Occasionally, during small movements of the knee joint, a joint receptor responded as if it were specialized to receive only one type of movement since it fired when the joint was moved in one direction through a certain angle but it did not respond when the joint was moved in the opposite direction through the same angle. Such results were not consistent, however, and in all such cases repeated examinations always showed that the particular receptor was capable of responding to both types of movement.

DISCUSSION

The data of Boyd and Roberts[1] give an impression of almost constant firing from joint proprioceptors, since in some cases proprioceptors fired continually at all joint angles which the investigators could produce, while in other cases only one threshold angle was reported. The data presented here, however, show that in all cases a receptor fired only during a relatively small range of the total flexion extension range of the joint. The rest of the time the receptor was silent. Apparently the data of Boyd and Roberts reflect only a portion of the total activity range of a proprioceptor, due to the restrictions of joint movement imposed by their experimental arrangement. The data reported here are in good agreement with those

obtained by Andrew and Dodt[6] when they recorded the activity of joint proprioceptors from the medial articular nerve.

At no time was a special fast adapting type receptor obtained which fired only in response to movement. Such receptors have been described,[4] although they represented only about 5% of all the proprioceptors recorded from the knee joint. Since the fast type receptor is rare, it is possible that purely by chance none was recorded from during the investigations reported in this paper. It may also be possible, however, that the fast adapting type response which has been described[4] was merely the response of a typical slow adapting proprioceptor which was receiving a very weak stimulus, such as that which might prevail when the joint is at an angle close to either of the threshold angles for that receptor. Andrew and Dodt have reported that when a stimulus was so weak that a receptor fired at less than 10 impulses per second, the firing soon ceased entirely.[2] Data reported here show that an ordinarily slow adapting receptor will occasionally show fast adaptation if the joint is stopped at a position which is just within the response range of a proprioceptor.

The receptors do not appear to be specialized to receive different types of movement. Certainly in regard to flexion-extension type movements a typical receptor responds to both. The fact that the precise threshold angles of a receptor are slightly different for flexion movements than they are for extension movements is probably due to the fact that the proprioceptors are situated in the joint capsule.[8] Thus they cannot be stimulated directly by the articulating surfaces but must rely for their stimulus upon the particular strains and stresses which develop in various parts of the capsule at each position of the joint.[5] It is not difficult to conceive in such an arrangement that a certain type of joint movement produces a particular amount of deformation within a given receptor, while another type of movement through the same angle produces a slightly different amount of deformation within the same receptor, and thus the response of the receptor would be slightly different in both cases. In a study of joint proprioceptors in the epiglottis, Andrew[1] concluded that there is only one type of joint proprioceptor but it is mounted on tissues which are differentially stretched and, consequently, some receptors fire during flexion only and others are activated by extension only. This is a good example of the type of mechanism which has been suggested above for knee joint proprioceptors to explain the differences in flexion-extension thresholds. This can also explain the apparent preference for one special type of movement which some knee proprioceptors exhibit, as reported by Boyd and Roberts.

It is quite possible, then, that only one type of proprioceptor exists in the knee joint of cats, and that its principal characteristics are slow adaptation, firing in response to a limited range of point angles, and activation by any type of joint movement or position which can effectively distort the area of the capsule in which the proprioceptor is situated.

SUMMARY

The activity of the knee joint proprioceptors was recorded from the posterior articular nerve in decerebrate cats in response to the full physiological range of flexion-extension type movements of the joint. The cat was held in a normal standing position and nerve activity was recorded with specially insulated *in vivo* electrodes.

Proprioceptive firing occurred at all angles of the knee joint.

Any individual proprioceptor had only a limited range of knee joint angles during which it fired.

The threshold angles for firing were quite precise and accurate for each proprioceptor investigated.

Once a proprioceptor was activated during a joint movement, its rate of firing usually increased until the joint reached a point of maximum sensitivity for that receptor, after which frequency usually decreased until it ceased entirely as the joint was moved beyond the sensitivity range of the receptor.

Static position of the joint at an angle which was within the sensitivity range of a receptor usually revealed very slow adaptation of the receptor. If the static angle was near either of the threshold angles for the receptor, adaptation was very rapid.

Threshold angles for a receptor were different depending on whether flexion or extension was employed. No evidence was obtained which indicated that special receptors existed for flexion or for extension.

It was suggested that there is one type of proprioceptor in the knee joint of cat and that activation of any given proprioceptor can be achieved when sufficient stress occurs in the area of the capsule in which the receptor is situated—the amount of stress at any instant depending on the particular angle of the joint and the direction, if any, in which the leg is being moved.

REFERENCES

1. Andrew, B. L.: Proprioception at the joint of the epiglottis of the rat. J. Physiol. (Lond.), 1954, *126*, 507–523.
2. Andrew, B. L. and Dodt, E.: The development of sensory nerve endings at the knee joint of the cat. Acta physiol. scand., 1953, vol. *28*, fasc. *1*, *287–297*.

3. Boyd, I. A.: Nerve impulses from proprioceptors in the knee-joint of the cat. J. Physiol. (Lond.), 1953, *119*, 8-9P.

4. Boyd, I. A. and Roberts, T. D. M.: Proprioceptive discharges from the stretch receptors in the knee-joint of the cat. J. Physiol. (Lond.), 1953, *122*, 38-58.

5. Cohen, L. A.: Nerve electrodes for in vivo studies. (Submitted for publication.)

6. Gardner, E.: The distribution and termination of nerves in the knee joint of the cat. J. comp. Neurol., 1944, *80*, 11-33.

7. Gardner, E.: Conduction rates and dorsal root inflow of sensory fibers from the knee joint of the cat. Amer. J. Physiol., 1948, *152*, 436-445.

8. Gardner, E.: Physiological mechanisms in movable joints. Amer. Acad. Orthopaedic Surgeons, 1953, *10*, 251-261.

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ELECTRICAL ACTIVITY AFTER STIMULATION AND ELECTROCOAGULATION OF THE HUMAN FRONTAL LOBE§

In his Salmon Lectures in 1950, Fulton[1] suggested that radical lobotomy should be abandoned in favor of more restricted lesions in the medioventral quadrant of the frontal lobe. Delgado and Rosvold[2] and Rosvold and Delgado[3] have shown that frontal lobe syndrome in the monkey may be produced by electrical stimulation or electrocoagulation of small areas in the head of the caudate nucleus, a structure which is within the limits of the medioventral quadrant of the frontal lobes.

As a form of therapy for human patients we have performed electrocoagulation of certain points in the frontal lobes which were selected after functional exploration by means of electrodes implanted within the brain for a period of several days. A discussion of the preceding work in animals[4] and of the technique[5] has been published elsewhere. Implanted electrode techniques in human patients have also been used by Brazier, *et al.*,[6] Heath,[7] and Sem-Jacobsen, *et al.*[8]

In this paper we submit information concerning electrical activity observed in the frontal lobes of nine patients after electrical stimulation and electrolytic destruction of selected points in these lobes.

MATERIAL AND METHODS

Five cases of schizophrenia, three of intractable pain, and one of anxiety neurosis were studied. Lobotomy had been recommended for these patients, and electrodes were implanted as a preliminary procedure in all of them and as alternative treatment in seven. The electrodes remained in the brain for the minimum time necessary for functional exploration and electrocoagulation. The average time was two and a half

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days; one case required four days; in another patient, operated upon under local anesthesia, 24 hours proved sufficient. In five patients, two multilead needle electrodes were placed in each side of the frontal lobes in the coronal-sphenoidal plane, 2 cm. anterior to the coronal suture. In the other four, one needle electrode was similarly placed in each frontal lobe, and one plate electrode was slipped below the dura over each side of premotor and motor cortex, providing a total of 24 leads. Additional data concerning this group of patients and information on spontaneous electrical activity will be published elsewhere.[7]

The needle electrodes were made of seven silver wires of graduated length, 0.1 mm. in diameter, insulated with Teflon. Four mm. of insulation were scraped from the tip of each of the seven wires; these contacts were spaced 8 mm. apart. The leads were cemented together with plexiglas and soldered to a subminiature seven-pin socket to form an electrode about 0.5 mm. in diameter. The plate electrodes were of similar delicate construction, the contacts being tiny balls on the ends of the silver wires which were encased in 1 mill gauge polyethylene sheet. Additional technical details may be found in a previous publication.[7] Needle and plate electrodes were placed in the brain through 2 cm. burr holes, with the patient under Pentothal-nitrous oxide general anesthesia. In one case a local anesthesia was used. Recording equipment included a Grass 8-channel electroencephalograph, a Grass stimulator type S-44, a DuMont dual beam oscilloscope type 321, tape recorder, and still and motion picture cameras.*

Electrical recordings and electrical stimulations were bipolar. Monopolar coagulations were performed through the same needle electrodes by applying 6 mA D.C. for about two minutes, using a constant current device designed by Mauro and Delgado.

RESULTS

Potentials evoked by single shock stimulation. A. Ipsilateral transmission. In patients having four needle electrodes it was possible to stimulate through the leads of one needle and to record from the leads of the other in each frontal lobe. In this way potentials evoked in the same side of the stimulated area were studied. A representative example is given in Figure 1. Recordings of electrical activity were taken from linkages 1-2, 3-4, and 5-6 of the right external electrode (RT EXT). Point 1 was always the deepest lead and point 7 the most superficial. Single, unidirectional square waves of 4 V. and 1 msec. pulse duration were applied every three seconds for about 30 seconds through different depths of the right medial electrode. The leads of both needle electrodes were at approximately comparable depths, the right external slightly deeper than the right medial.

Single shocks, delivered between leads RT MD 1-2 (the deepest), evoked a spike followed about 50 msec. later by a sharp wave in leads RT EXT 1-2. The stimulus artefact was visible in the other two channels, but the evoked response was small in linkages RT EXT 3-4 and was absent in

* The motion picture was presented at the Fifth International Congress of Neurology, Lisbon, 1953.[9]

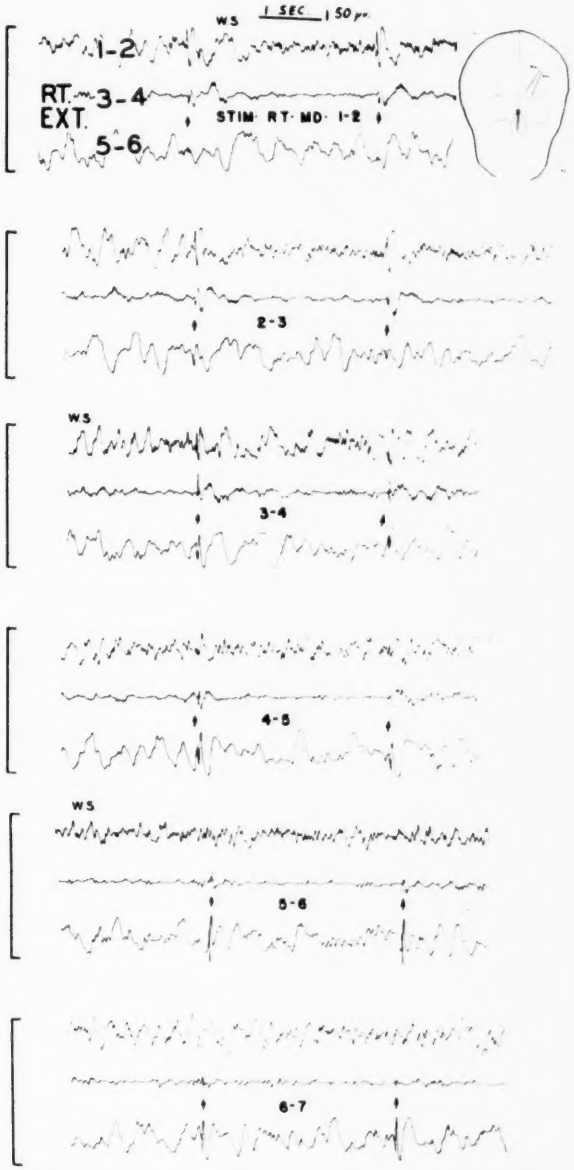

FIG. 1. Ipsilateral transmission of evoked potentials. Recording linkages through the right external needle electrode (RT. EXT.) were kept constant. At the arrows single shock stimulation was applied through different leads of the right medial electrode (RT. MD.) as indicated in the recordings. In all figures lead 1 was deepest, lead 7 most superficial.

RT EXT 5-6. Electrical stimulation through intermediary points evoked responses which were more noticeable from the recording leads located approximately at the level of the stimulating leads. When stimulation was applied through the most superficial points, RT MD 6-7, the evoked response was apparent in the most superficial leads and absent in the deepest points of the right external electrode.

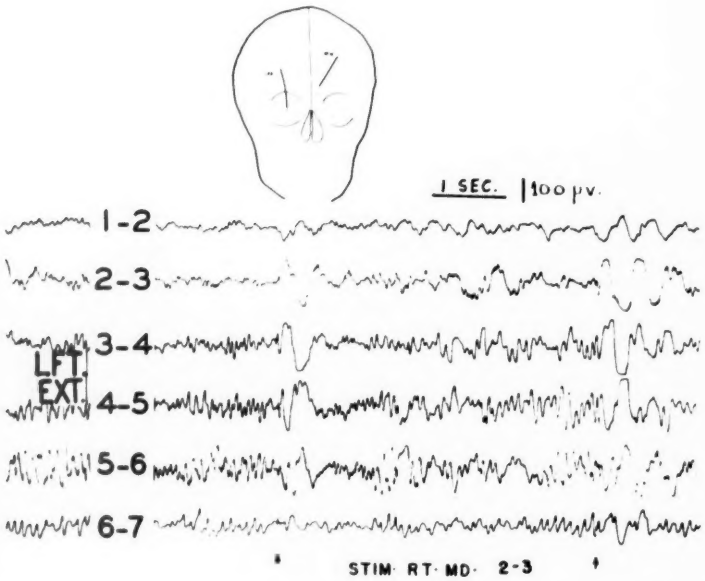

FIG. 2. Contralateral transmission of evoked potentials. Recording through the left external electrode (LFT EXT). At the arrows single shock stimulation through leads 2-3 of the right medial electrode (RT MD). Observe reversals between leads LFT EXT 3-4 and 4-5.

B. Contralateral transmission. When single shocks were delivered to one side of the frontal lobes and recordings were taken from the other side, responses consisted in general of a small sharp wave followed by one or more slow waves of decreasing amplitude. The evoked potentials mainly affected areas deeper or more superficial, according to the relative position of the stimulating points. An example is given in Figure 2 in which recordings were taken from the left external electrode (LFT EXT) and single unidirectional square waves of 4 V. and 1 msec. pulse duration were applied at the arrows, leads RT MD 2-3. Highest amplitude of response and

reversals were found in linkages 3-4 and 4-5, which were at a depth comparable to the stimulating leads. The evoked response was minimal at the deepest (LFT EXT 1-2) and at the most superficial (LFT EXT 6-7) linkages.

The amplitude of the evoked potentials was related to the voltage of stimulation without affecting the delay of the response in general. An example is shown in Figure 3. Electrical stimulation was applied in the depth of the right frontal lobe and oscilloscopic recordings were taken from the left side. Leads of the upper channel were at about the same depth as the stimulating points. Leads of the lower channel were about 10 mm. higher. Stimulation was increased two volts at a time from 2 to 8 V. The delay of the slow wave response in the first channel was about the same at all voltages tested (a little over 200 msec.). Amplitude of evoked responses increased when the stimulating voltage was augmented. At 8 V. the first slow wave was followed by another one of less amplitude and similar duration.

Effects of repetitive stimulation on electrical activity. Frequency of pulses 60-100 c/sec., pulse duration 0.1-1 msec., and voltages up to 30 for 5-10 seconds were tested in all the patients at different depths of the frontal lobes. Electrical stimulation within the frontal lobes using 100 c/sec., 1 msec. pulse duration and 10 V. for 5-10 seconds often evoked afterdischarges in both sides of the frontal lobes (Fig. 4) which lasted for 5-60 seconds and were followed by slow waves for a period of a few minutes in the stimulated side. A quick return to the pre-stimulation pattern was usual in the nonstimulated side. The pattern of afterdischarge generally showed high voltage, irregular activity of 1 to 8 c/sec. and occasionally high voltage rapid spikes. Patterns different in frequency and amplitude occurred at different depths. Wave and spike activity was less often observed. Afterdischarges were evoked with lower thresholds in the superficial than in the deep points of the frontal lobes. At threshold levels of stimulation the afterdischarge might be limited to the stimulated side only, and on a few occasions to only the stimulated point. The afterdischarges more often spread to superficial than to deep areas. In some cases it was possible to see all points of the stimulated side and the two or three most superficial of the other side involved in an afterdischarge, while the electrical activity around the deepest points of the nonstimulated side remained undisturbed. Often, when several afterdischarges had been evoked, it was possible to trigger the corresponding side by electrical stimulation of some previously unresponsive areas. For example, in one patient stimulation of RT NDL 1-2 with 60 c/sec., 1 msec. pulse duration, and 5 V. for 10 seconds produced no effect.

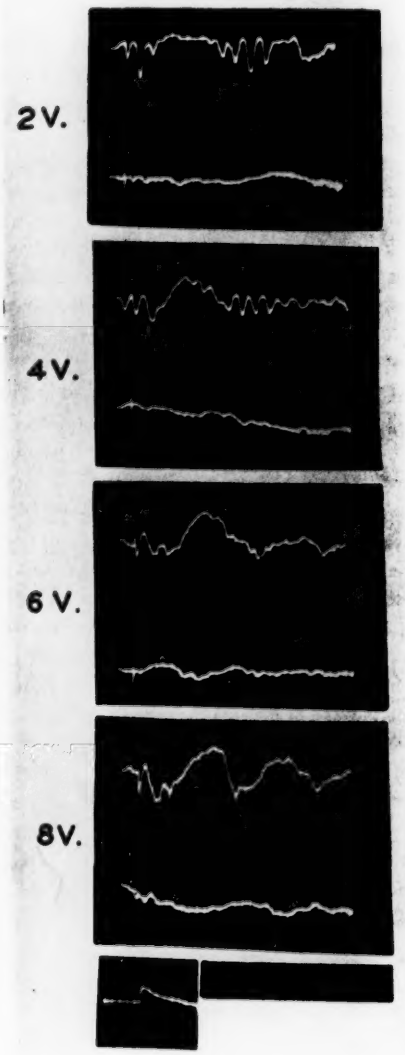

FIG. 3. Single shock stimulation with increasing voltages was applied in the depth of the right frontal lobe. Leads connected to the upper channel were in the left frontal lobe at about the same depth as the stimulating points. Leads connected with the lower channel were in the left frontal lobe 16 mm. higher. Observe in the upper channel the increase in amplitude of response without modification of delay. In the lower channel there was no response. Calibration: 50 μV., 0.1 sec.

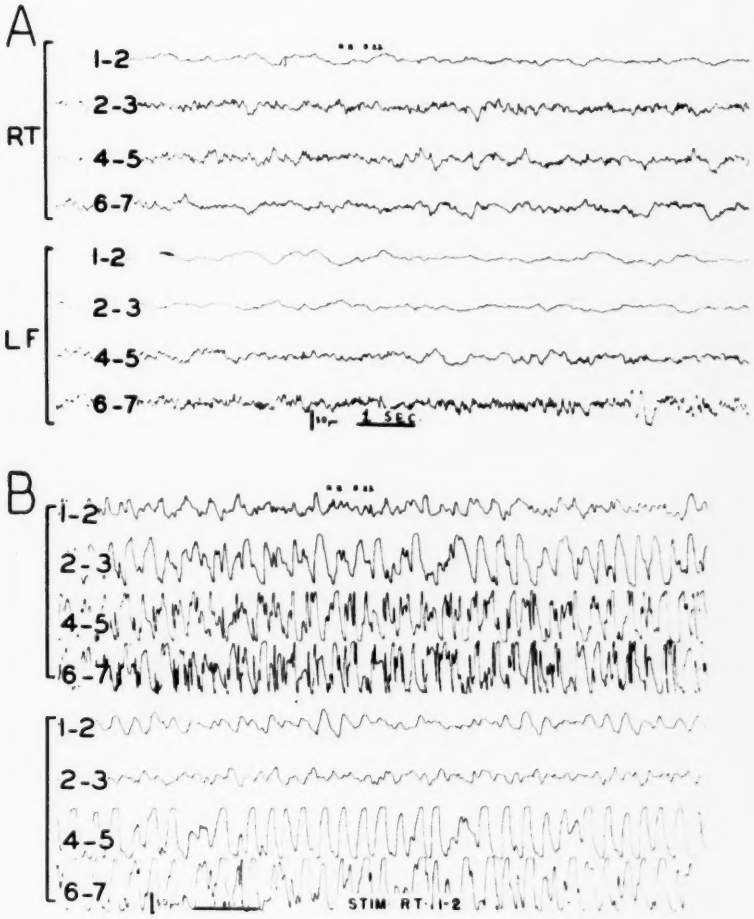

FIG. 4. *A.* Spontaneous electrical activity of the frontal lobes before stimulation. *B.* Electrical stimulation through leads 1-2 of the right external electrode evoked an afterdischarge which in this case affected both sides of the frontal lobes. Behavior, conversation, and motor activity of the patient were not modified during the afterdischarge.

Then points LFT NDL 5-6 and 6-7 were stimulated with the same parameters and several afterdischarges were evoked. A few minutes later stimulation of RT NDL 1-2 was repeated with the same parameters and one afterdischarge of about 20 seconds' duration was evoked in all linkages of the *left* frontal lobe, without modification of the electrical activity of the right

side. Afterdischarges evoked by electrical stimulation of the frontal lobes were in general restricted to this area of the brain, as evidenced by plate recordings from other areas. However, in some instances, especially when high voltages were used and the most superficial points stimulated, the evoked activity spread to the premotor and motor areas and was recorded directly from these regions through the plate electrodes. The spread of seizure activity from the frontal lobes to the motor area was a slow process, requiring several seconds to reach the ipsilateral motor area and longer to affect the contralateral motor area. The development of a seizure pattern in these regions was also slow and often took 20 or more seconds to show well organized waves and spikes. The end of the seizure activity was independent in both areas. In general it ended first in the frontal lobes and was succeeded by slow waves, while the motor area was still producing waves and spikes at full strength.

Effect of evoked afterdischarges on the patients. General behavior, motor activity, and conversation were not apparently modified by afterdischarges localized to the frontal lobes. One patient, for example, was looking at a magazine and making pertinent comments to the interviewer. Electrical stimulation of point RT MD 1-2 (100 c/sec., 1 msec. pluse duration, 25 V. for 5 secs.) evoked one afterdischarge of 15 seconds' duration affecting both frontal lobes, and was followed by slow waves which lasted about five minutes in the right frontal lobe. During all this time the patient continued looking at the magazine, turning pages and talking with the interviewer, who did not observe any change. The normality of the behavior of the patient was in marked contrast to the gross abnormalities in the electrical activity of his frontal lobes. On the contrary, in a few cases in which the afterdischarges spread from the frontal lobes to the motor cortex, a motor seizure with loss of consciousness followed. The patients were out of contact for one or two minutes and then seemed to recover completely while the electrical activity of the frontal lobes still showed slow swings away from the pre-seizure pattern. One patient was stimulated (RT EXT 1-2; 100 c/sec., 1 msec., 10 V. for 5 secs.) while he was reciting poetry. He suddenly stopped; when stimulation was discontinued, he commented that he had felt a funny sensation in the head and was unable to think of the words of the verse. "My mind was blank," he said, "as if I had drunk a lot of beer." This effect was repeated several times and tape recorded. Fake stimulations and stimulations of other points failed to produce the described sensation. In other patients stimulation of different points evoked motor, sensory, and autonomic effects, which will be described in another publication.

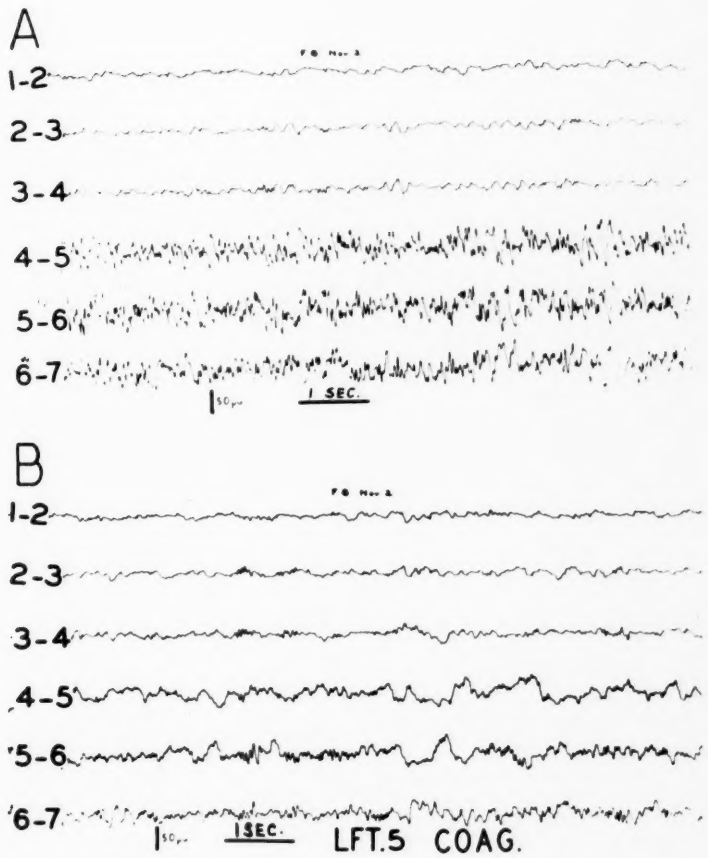

FIG. 5. *A.* Spontaneous electrical activity of the left frontal lobe before electrocoagulation.

B. General reduction in the spontaneous electrical activity of the left frontal lobe followed electrocoagulation of point 5 of the left needle electrode.

Electrocoagulation. The points to be electrocoagulated were selected after studying their spontaneous electrical activity and the results of electrical stimulation. It was done in the fully conscious patient while he was being interviewed. Recordings of electrical activity were made immediately before and after coagulation of each point. The patients were unaware that the final step was being taken and possible psychological factors were thus avoided. Six to ten points were routinely coagulated in each case and the following phenomena were observed:

(i) No change in the basic electrical activity of the frontal lobe.

(ii) General reduction in the amplitude of the spontaneous electrical activity of the homolateral frontal lobe (Fig. 5). The electrical activity of the other side was not altered until a similar contralateral point was electrocoagulated.

(iii) Slow waves and pulsation artefacts sometimes followed the destruction, lasting from several minutes to hours.

(iv) In two patients believed to be suffering from intractable pain, immediate but temporary improvement appeared to occur, which was coincidental with modification of electrical activity in the focal area of electrocoagulation.

DISCUSSION

In both cats and monkeys single shock stimulation of a cortical point may induce a localized electrical response at the corresponding point of the opposite hemisphere, according to Curtis and Bard.[3] In the same way local strychninization of a cortical point may fire the corresponding point in the opposite hemisphere, according to McCulloch.[10] Chang[2] also found in the cat a localized electrical response in a symmetrical point, contralateral to the stimulated cortex, especially in the suprasylvian cortex. In the present study single shocks applied within the frontal lobes in unanesthetized human patients evoked potentials which were recorded preferentially from leads located at a similar depth, as shown in Figures *2* and *3*. These findings suggest that pathways in the explored area of the frontal lobes are not diffusely projected systems, and are oriented horizontally. In the ipsilateral recordings the evoked potentials could be caused by a spread of current from the stimulating leads to the area recorded, but even in this case the absence of diffuse responses would support the hypothesis of well organized pathways with delimited projections.

In contralateral recordings the initial sharp wave having a delay of a few milliseconds (Fig. 3) could be related to callosal transmission, and the slow wave having a delay of over 200 milliseconds to longer circuits with probable thalamic participation. It was interesting to observe that when intensity of stimulation was increased, the delay of the slow wave response was not modified and only the amplitude was greater.

When repeated stimulations of the frontal lobes evoked afterdischarges propagated to the premotor and motor areas, the onset and end of the

* The diagnosis of one patient was taboparesis and of the other, thalamic pain due to a stroke. Transient pain relief in these individuals following focal interomedial electrocoagulation in the frontal lobe may simulate the more lasting improvement obtained in similar cases after uni- or bimedial lobotomy.

seizure activity were often independent in the two regions, with a rather slow propagation from one area to the other. This finding indicates that, at least in some cases, afterdischarges are dependent upon local activity and not upon a general pacemaker. Both frontal lobes could be involved in afterdischarges without apparent modification of the behavior of the patients, as contrasted to the loss of consciousness which accompanied similar afterdischarges of the motor areas. The pioneer work of Fulton and Jacobsen[1] and the considerable work accumulated afterwards (see bibliography in Greenblatt and Solomon[2]) proved that frontal lobes are not essential for consciousness but play an important rôle in behavior. However, according to our observations, disturbances of their electrical activity may not be registered in overt behavior.

The ipsilateral reduction of spontaneous electrical activity of the frontal lobes after electrocoagulation of some points seems to indicate (a) the independence of the origin of electrical activity in the two hemispheres, and (b) the importance of some points for the electrical activity of a wide area.

SUMMARY

Exploration and therapeutic electrocoagulation of discrete points in the frontal lobes was done by means of multilead electrodes implanted within the brains of nine patients for periods of one to four days. Potentials evoked by electrical stimulation were recorded at different depths of the ipsi- and contralateral frontal lobes. Conclusions follow:

1. Responses evoked by single shock stimulation consisted in a spike or sharp wave followed by one or more slow waves.

2. Evoked potentials were recorded mainly from contacts located at about the same depths as the stimulating points. This suggests that pathways within the frontal lobes are organized without diffuse projecting systems and are horizontally oriented.

3. Repetitive stimulation of the frontal lobes with appropriate parameters evoked afterdischarges which, depending upon the intensity of stimulation, were limited to one point, to one side, or to both sides of the frontal lobes.

4. The evoked electrical disturbance of the activity of the frontal lobes did not modify behavior, conversation, or motility of the patients except in the few cases in whom the evoked afterdischarges of the frontal lobes spread to the motor areas, producing a motor seizure with loss of consciousness.

5. Electrocoagulation of different points of the frontal lobes could produce the following effects upon its electrical activity: (a) no effect; (b) ipsilateral general reduction of amplitude; (c) slow waves.

REFERENCES

1. Brazier, M. A. B., Schroeder, H., Chapman, W. P., Geyer, C., Fager, C., Poppen, J. L., Solomon, H. C., and Yakovlev, P. I.: Electroencephalographic recordings from depth electrodes implanted in the amygdaloid region in man. EEG clin. Neurophysiol., 1954, *6*, 702.
2. Chang, H-T.: Cortical response to activity of callosal neurons. J. Neurophysiol., 1953, *16*, 117.
3. Curtis, H. J. and Bard, P.: Intercortical connections of the corpus callosum as indicated by evoked potentials. Amer. J. Physiol., 1939, *126*, 473.
4. Delgado, J. M. R.: Permanent implantation of multilead electrodes in the brain. Yale J. Biol. Med., 1952, *24*, 351.
5. Delgado, J. M. R.: Study of some cerebral structures related to transmission and elaboration of noxious stimulation. J. Neurophysiol., 1955a, *18*, 261.
6. Delgado, J. M. R.: Evaluation of permanent implantation of electrodes within the brain. EEG clin. Neurophysiol., 1955b. (In press)
7. Delgado, J. M. R. and Hamlin, H.: Surface and depth electrography of the frontal lobe in conscious patients. EEG clin. Neurophysiol. (accepted for publication).
8. Delgado, J. M. R., Hamlin, H., and Chapman, W. P.: Technique of intracranial electrode implacement for recording and stimulation and its possible therapeutic value in psychotic patients. Confin. neurol. (Basel), 1952, *12*, 315.
9. Delgado, J. M. R. and Rosvold, H. E.: Effect on intelligent behavior of stimulation or destruction of pathways in the frontal lobes of monkeys. Fed. Proc., 1953, *12*, 32.
10. Fulton, J. F.: *Frontal lobotomy and affective behavior*. New York, W. W. Norton and Co., Inc., 1951. 159 pp.
11. Fulton, J. F. and Jacobsen, C. F.: The functions of the frontal lobes, a comparative study in monkeys, chimpanzees and man. Advances in mod. Biol. (Moscow), 1935, *4*, 113.
12. Greenblatt, M. and Solomon, H. C.: *Frontal lobes and schizophrenia*. New York, Springer Publishing Co., Inc., 1953. 425 pp.
13. Hamlin, H., Delgado, J. M. R., Chapman, W. P., and Rosvold, H. E.: Therapeutic interruption of frontal fibertracts by electrolysis. Trans. Vth int. Congr. Neurol. (Lisbon), 1953, p. 406.
14. Heath, R. G.: *Studies in schizophrenia*. Cambridge, Harvard University Press, 1954. 619 pp.
15. McCulloch, W. S.: Cortico-cortical connections. Pp. 212-242 in: Bucy, P. C., Ed., *The precentral motor cortex*. Urbana, University of Illinois Press, 1944.
16. Rosvold, H. E. and Delgado, J. M. R.: The effect of delayed alteration test performance of stimulating or destroying electrically structures within the frontal lobes of the monkey's brain. J. comp. physiol. Psychol., 1956 (in press).
17. Sem-Jacobsen, C. W., Petersen, M. C., Lazarte, J. A., and Dodge, H. W., Jr.: Electroencephalographic rhythms from the depths of the frontal lobe in 60 psychotic patients. EEG clin. Neurophysiol., 1955, *7*, 193.

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MOTOR REPRESENTATION IN THE FRONTAL SULCI OF THE CAT‡

We were privileged to make our debuts in neurophysiology at Yale under the inspiring guidance of Professor John Fulton. While still very "wet behind the ears" we began together to study visceral and somatic motor representations throughout the frontal lobes of various experimental animals. Dr. Fulton was especially encouraging to us when we began to investigate the cortex hidden within the depths of frontal sulci. He pointed out that there was no reason to suppose *a priori* that the functions of cortex buried within the sulci were generically different from or less significant than those already attributed to the more accessible and therefore better known surface areas. Our first paper therefore included an analysis of the representation of respiratory movements within the frontal sulci of the anesthetized dog and monkey. Although we extended observations relating to hidden cortex to other animals, including the chimpanzee, we recognized the desirability of mapping buried cortex systematically as an aid to preliminary localization during aseptic implantations of electrodes for later analysis in waking, freely moving animals without anesthesia. We considered that hidden cortex should be thoroughly explored in cats because of their general availability and their adaptability to the Horsley-Clarke stereotaxic apparatus.

Although many have emphasized the importance of taking hidden cortex into consideration in accounting for the total cortical representation in cats, there is as yet no schema available which indicates the general functional organization of this extensive and relatively inaccessible region. Some previous studies were helpful in supplying information relating to fragmentary parts of the hidden motor cortex (see Delgado, 1952, for a review of the literature), but often these data were obtained after surgical ablation of one bank of the sulcus concerned. Surgical exposure of the surface of buried cortex has the advantage of direct observation of electrical placements, but

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has the disadvantage of imposing some circulatory embarrassment to the stimulated site and of limiting cortico-cortical relations which may be important in support of background activity as well as in the cortical organization of the motor response. We were fortunate in having access to a Horsley-Clarke apparatus whereby we could test responses to stimulation of carefully tapered bipolar concentric electrodes which penetrated the brain millimeter by millimeter. This technique is not itself free from some disadvantages, but we looked upon it as an improvement over surgical exposure and it did have the advantage of simulating conditions which are encountered during operative implantation of electrodes.

METHODS

Twenty cats, lightly anesthetized with Dial, were fixed to a Horsley-Clarke stereotaxic instrument and then suspended, instrument and all, from a horizontal bar, so that the four extremities were dangling and the lateral movements of the head and trunk could be readily detected. Twenty-gauge bipolar concentric probing electrodes, insulated except at the bared end of the shaft and tip of the internal electrode, were utilized for mapping millimeter by millimeter in successive vertical columns throughout the frontal lobes. By making use of both hemispheres, six to twelve such vertical tracts could be studied in each animal. Rectangular and thyratron discharge pulses were used for stimulation. Responses were detected visually and by palpation. Electrode tracts were identified by gross and microscopic brain sections, a paraffin coated thread being placed in each of the successive electrode tracts during the experiment and removed again only after the brain had hardened.

RESULTS

Figure 1 is a diagrammatic synthesis of our data concerning the motor functions of the hidden cortical surfaces. In addition to the representations indicated, hind limb responses were obtained by stimulating the surface of the posterior sigmoid gyrus, forelimb and face responses by excitation of the anterior sigmoid gyrus, and movements of the face, tongue, mouth and eyes evoked from the anterior portions of the coronal and diagonal gyri. Moreover, the surface cortex around the middle portion of the coronal sulcus yielded trunk and hind limb movements. There appeared to be a continuum of motor representations which extend throughout both the surface gyri and cortex hidden within the sulci. Some cats, seeming to have less extensive representation of motor functions on the exposed surfaces of the hemisphere, proved to have greater than usual representation within buried cortex. Although slight variations from animal to animal occurred, there was a clear homology between one hemisphere and the other in each individual experimental animal. Certain facts relating to responses evoked from hidden cortex of the frontal lobe sulci in the cat seem worthy of detail.

Sulcus cruciatus. The cortex hidden within this sulcus is approximately 120 mm² in extent. In general, stimulation within this area yielded slow flexion of the contralateral hind limb. By employing currents only ten per cent above threshold for barely discernible responses, discrete individual movements which were characteristic for particular loci could be elicited. These involved motion of the pelvis, thigh, foot and paw, including the digits and claws. The movements were expressed in rotation, abduction, adduction, extension and flexion (the latter especially readily obtainable from the ventral bank of the sulcus), of the proximal parts of the limb, and digital extension, flexion or fanning, with claw presentation or retraction. Occasionally both hind limbs responded to cruciate sulcus stimulation; purely ipsilateral responses were rare. There were also points near the anterior extent of the cruciate sulcus which yielded pelvic tilting with or without accompaniment of hind limb movements. Nearby some loci gave combined movements of fore and hind limbs. Contraction of spinous muscles on the side opposite to the hemisphere stimulated caused trunk movements which sometimes spread to involve extension of the contralateral hind limb. In addition, tail movements were elicited by stimulation of the cruciate sulcus. These usually took the form of slow elevation from a relaxed dependent position to a nearly horizontal plane.

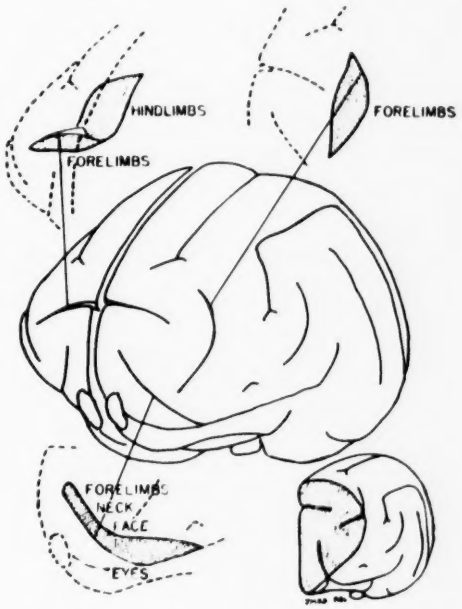

FIG. 1. Diagrammatic representations of motor functions of the hidden cortical surfaces. *Superior left*, sulcus cruciatus; *superior right*, sulcus coronalis; *inferior left*, sulcus presylvius; *inferior right*, diagram of the three sulci in a coronal section.

Cruciate sulcus movements were obtained quite consistently in all twenty cats and in the same pattern of representation within the sulcus. The anterior two thirds of the sulcus had somewhat lower thresholds for

response and evoked more prompt and imperious movements. Responses elicited from the posterior one-third of the sulcus tended to be less discrete, less uniform in timing and in the characteristics of motor display, and to be less readily fatigued.

Sulcus coronalis: There are approximately 80 mm² of hidden cortex within the two banks of this sulcus. Stimulation of the anterior portion induced lifting of the contralateral wrist and curling flexion of the paw. Sometimes contralateral flexion and ipsilateral extension were observed. Additional responses from different points within this region included pronation, supination, adduction and abduction of the contralateral or of both forelimbs. The posterior half of this sulcus required relatively higher intensities of stimulation and the responses were more complex and less consistent from trial to trial.

Sulcus presylvius: There are about 125 mm² of cortex enclosed by this sulcus. Since its course is practically vertical, electrodes can pass along its length from the base of the inverted "U" to its opening onto the antero-ventral surface of the brain. Forelimbs are represented in the superior part of the sulcus, extension toward the topmost part and flexion a little deeper. Although most responses were contralateral, some were bilateral and, more rarely, ipsilateral alone. Rhythmic "pawing movements" were also evoked, the cycle being repeated again and again during continuous stimulation. Head turning was elicited below forelimb responses. In two animals, stimulation of the middle portion of the sulcus presylvius caused acceleration of respiration and gutteral vocalization.

Face representation is widespread throughout the inferior half of the presylvian sulcus. Facial responses here were lower in threshold than any other somatic movements obtained from deep or surface stimulation. The forward or upward movement of vibrissae had the lowest threshold of any facial response. In addition to tonic sustained movements of the vibrissae, rhythmic responses were often observed in which the whiskers twitched forward and then dropped more slowly backward, the rhythm varying from one to ten per sec. according to the applied stimulus strength. We referred to these as "vibrissae nystagmus." Vibrissae and eyebrow or vibrissae and forelimb responses occurred commonly from stimulation of single loci.

Eye movements, usually conjugate in the vertical or horizontal plane and usually accompanied by opening or closing of the eyelids or other facial movement, were elicited from the inferior part of this sulcus. An eye field functionally comparable to that of the monkey's area 8, however, appears to lie on the medial surface of the frontal lobe of the cat.[10,16] Pupillary dilatation occurred predominantly but not exclusively on excitation of the

middle and inferior portions of the medial bank of this sulcus. Stimulation of the medial bank of the presylvian sulcus caused inhibition of respiration, resulting in shallow, slow respiration or arrest in the expiratory position. Confirming Hess, *et al.*,[7] we found that the lower parts of the lateral bank of the sulcus yielded responses of the jaw and tongue, with some rhythmic movements, including opening and closing of the mouth, chewing, lapping, or swallowing. Swallowing usually accompanied lapping or chewing responses, but sometimes it occurred independently with a repetition of the swallowing sequence throughout the duration of stimulation. Occasionally there were isolated movements of the tongue such as curling or protrusion. At a few locations salivary secretion could be observed to increase distinctly during stimulation.

Although there were some variations in the maps of sulcus presylvius as analyzed in different cats, two features of the responses were remarkably consistent: the two hemispheres were closely matched in any one cat and the sequence of representation along the sulcus was the same throughout the series. Ascending the lateral column of the inverted "U" from its ventral to its dorsal parts, we found tongue, jaw, swallowing, vibrissae, face, eyelid and eye movements, neck and finally forelimb responses near the top of the "U." On descending the medial bank of the sulcus we encountered an extensive zone yielding forelimb movements, then pupillary and respiratory changes.

DISCUSSION

It has already been emphasized by several physiologists that functions probably do not stop abruptly at the margins of sulci or "jump across" to the opposite sulcal margin, but that they may continue within the hidden cortex in the depths of the sulcus. Stout, over forty years ago, attempted to explore the banks of the cruciate sulcus and did obtain discrete somatic responses which were different for the anterior and posterior banks of the sulcus. But he complained of the great difficulty of its exploration because of the location of an artery lying between the two lips of the sulcus.[8] Magoun, Ranson and Fisher stated in 1933 that "while only incidental information is furnished by the present series of experiments on the demarcation of the cortical motor area of the cat, the large number of responses obtained from buried cortex forming the lateral and dorsal wall of the presylvian sulcus is of interest."[9] Carol, in 1942, indicated that in the cat "There was no region from which responses of the trunk could be obtained until the intensity of the stimulus was sufficiently high to produce a spread of current and simultaneous movements of either the fore- or hind limb or

both. Such an area may lie in the depths of the *sulcus cruciatus*.'" Sugar, Chusid and French explored the depths of the sylvian and lunate sulci in the monkey by making a surgical exposure of the buried cortical surfaces. They acknowledge the difficulties and disadvantages of this method. Chusid, Mahoney and Robinson, also using surgical exposure techniques, investigated the motor functions of the hidden cortex in the frontal lobe of the dog,[8] and Wilbur Smith made a similar examination in the cat[9], but apparently these studies were published only in abstract. Because of the inconveniences of mapping this infolded territory, Woolsey and his associates have given their principal attention to investigations of the more primitive brains.[6] In higher primates, Leyton and Sherrington found "the portion of the motor region which lies buried in the sulcus centralis and other fissures amounts to not less than about 35 per cent of the whole motor region."[5] Hidden cortex becomes a progressively larger fraction of the total cortex in higher mammals,[3] and it is reasonable to suppose that motor representation in man will eventually need to be understood in terms of the hidden as well as surface cortex.

Although our observations were confined to the overt responses which could be evoked by stimulation of the surface and depths of the frontal lobe, we are well aware that movements might be aroused by stimulation of regions that are essentially sensory in function. In fact, the higher thresholds, less confined and uniform (less evidently imperious) responses encountered in the posterior portions of the cruciate and coronal sulci suggested to us that we were stimulating what might be predominately "sensory fields." Our inclination is to consider all of the frontal lobe territory from which responses may be elicited, both superficial and deep cortex, as "sensorimotor" in character.

At times our penetrating electrodes were located in white matter from which motor responses were readily elicitable. Our report, however, has been confined to the identification of responses which were induced while the electrodes were in place within, or in close contact with, cortical grey substance. We have the impression that cortical responses, as contrasted with responses from white matter, are of lower threshold and exhibit a greater continuity of functional representation among adjacent points. In addition to providing useful information for the problem of electrode implantation, these data suggest to us the importance and dignity deserving in our consideration of the role of cortex buried within sulci. Rather than having this imply still another (fourth or fifth) motor zone, we would prefer to consider the entire sensorimotor region as being unitary and continuous over the surface and into the depths of the sulci as well.

SUMMARY

Cortex hidden within enclosed portions of the sulci cruciatus, coronalis and presylvius, has been stimulated electrically in twenty cats under Dial anesthesia by means of bipolar concentric electrodes directed stereotaxically so as to penetrate the frontal lobe millimeter by millimeter.

The hidden cortex forming the walls of these sulci in each hemisphere has a combined extent of more than three hundred square millimeters, an area comparable to the surface extent of the frontal lobe of the cat. Throughout subsurface cortex there is an important and essentially continuous "sensorimotor" region from which discrete somatic motor movements may be evoked.

Stimulation of the cortex within the cruciate sulcus yields movements of the contralateral hindlimb, trunk and tail. There is a small region of forelimb representation in the anterior part of this sulcus. Forelimb responses are also elicitable from the anterior part of sulcus coronalis. Within the sulcus presylvius there is an extensive motor representation of the anterior half of the animal: forelimbs near the top, head and neck movements, face, vibrissae, eyelid and eye movements, jaw, tongue, pupillary and respiratory responses as the orbital surface is reached. There are differences in representation within the opposing surfaces of each of these three sulci and each bank appears to provide a series of motor representations which are continuous with those encountered on stimulation of the surface gyri.

ACKNOWLEDGMENT

A good part of our published work, including the present one, has received support, encouragement, and constructive ideas from Dr. Fulton, and we should like to express to him our warm appreciation for his constant help and advice.

REFERENCES

1. Clusid, J. G., de Gutierrez-Mahoney, C. G., and Robinson, R.: The "motor" cortex of the dog. Fed. Proc., 1949, *8*, 25.
2. Clusid, J. G., Sugar, O., and French, J. D.: Commissural connections of cerebral cortex lying within arcuate and lunate sulci of monkey (Macaca mulatta). J. Neuropath., 1948, *7*, 439.
3. Delgado, J. M. R.: Hidden motor cortex of the cat. Amer. J. Physiol., 1952, *170*, 673.
4. Delgado, J. M. R.: Permanent implantations of multilead electrodes in the brain. Yale J. Biol. Med., 1952, *24*, 351.
5. Delgado, J. M. R. and Livingston, R. B.: Some respiratory, vascular and thermal responses to stimulation of orbital surface of frontal lobe. J. Neurophysiol., 1948, *11*, 39.
6. Garol, H. W.: The "motor" cortex of the cat. J. Neuropath., 1942, *1*, 139.
7. Harman, P.: On the significance of the fissuration of the isocortex. J. comp. Neurol., 1947, *87*, 161.

8. Hess, W. R.: Korrespondierende Symptome aus Stirnhirn, Innerer Kapsel und vorderem Thalamus. Helv. physiol. pharmacol. Acta, 1948, *6*, 731.

9. Hess, W. R. and Akert, K.: Die corticale Repräsentation von Gesicht, Oral- und Pharyngealsphäre bei der Katze. Helv. physiol. pharmacol. Acta, 1951, *9*, 269.

10. Hess, W. R., Akert, K., and McDonald, D. A.: Beziehungen des Stirnhirnes zum vegetativen System. Helv. physiol. pharmacol. Acta, 1951, *9*, 101.

11. Hess, W. R., McDonald, D. A., and Livingston, R. B.: Head turning and eye deviation evoked by cortical excitation in the freely moving cat. Fed. Proc., 1951, *10*, 63.

12. Hodes, R. and Magoun, H. W.: Autonomic responses to electrical stimulation of the forebrain and midbrain with special reference to the pupil. J. comp. Neurol., 1942, *76*, 169.

13. Hodes, R. and Magoun, H. W.: Pupillary and other responses from stimulation of the frontal cortex and basal telencephalon of the cat. J. comp. Neurol., 1942, *76*, 461.

14. Kaada, B. R.: Somato-motor, autonomic and electrocorticographic responses to electrical stimulation of "rhinencephalic" and other structures in primates, cat and dog. Acta physiol. scand., 1951, *23* (suppl. 83), 1.

15. Leyton, A. S. F. and Sherrington, C. S.: Observations on the excitable cortex of the chimpanzee, orang utan, and gorilla. Quart. J. exp. Physiol., 1917, *11*, 135.

16. Livingston, R. B.: Localization of frontal oculomotor cortex in the cat. Fed. Proc., 1950, *9*, 395.

17. Magoun, H. W., Ranson, S. W., and Fisher, C.: Corticofugal pathway for mastication and other motor functions in the cat. Arch. Neurol. Psychiat. (Chicago), 1933, *30*, 292.

18. Smith, W. K.: Electrically responsive cortex within the sulci of the frontal lobe. Anat. Rec., 1940, *76* (suppl.), 75.

19. Spencer, W. G.: The effect produced upon respiration by faradic excitation of the cerebrum in the monkey, dog, cat and rabbit. Philos. Trans. B, 1894, *185*, 609.

20. Stout, J. D.: On the motor functions of the cerebral cortex of the cat. Psychobiol., 1917, *1*, 177.

21. Woolsey, C. N.: Patterns of localization in sensory and motor areas of the cerebral cortex. Chapter 14 in: *The biology of mental health and disease*. New York, Hoeber, 1952, 654 pp. (193-206).

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THE TWO-STAGE "PROTHROMBIN" ASSAY IN STUDY OF BLEEDING AND CLOTTING DISORDERS§

Recent study of 400 human cases, including 240 with diverse hemorrhagic disorders, has accumulated noteworthy experience with a wide variety of test methods for quantitating the collective and individual factors in the blood clotting and hemostatic mechanisms. Important among these tests are those dealing with prothrombin and its conversion to thrombin for the enzymatic polymerization of fibrinogen to fibrin clot. The so-called "prothrombin time" test, originated by Quick *et al.*,[1] has been compared in this investigation with three specific prothrombin methods. Ware and Seegers[2] made detailed studies of the technical aspects of the "2-stage" prothrombin assay method originated by Warner, Brinkhous, and Smith.[3] The present communication deals with our experience bearing on the validity of this method and its modifications, including some of our own, based upon experiments of a technical nature, with the opportunities for using test plasmas and sera from a representative collection of cases with bleeding disorders.

MATERIALS AND METHODS

Blood is obtained from an arm vein using a siliconed syringe. Some is clotted in glass at 37° C. and after 1 hour is mixed with 1/10 vol. of 0.1 M sod. oxalate and centrifuged for the *serum*, which is used in the *prothrombin consumption test*. This test gives the percentage loss of prothrombin after 1 hour at 37° C. as computed from assays on serum and the corresponding plasma (see below). Another blood sample is oxalated immediately and centrifuged for *plasma*, which is used for many tests. "One-stage" methods[4] following a basically similar procedure are: (a) *prothrombin time* (PT) test, (b) *specific prothrombin assay* (Method I), (c) *specific fibrinogen assay*

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assay, (d) *specific proaccelerin assay*. The common procedure is to time the clotting at 37° C. after adding 0.2 ml. Ca tplh. to the various plasma mixtures. "Ca-tplh." is equal vols. of 0.02 M $CaCl_2$ and tissue thromboplastin, the preferred preparation being "soluplastin,"* since our tests show this to be free from (pro)convertin and (pro)-accelerin contaminants. The respective "substrates" are: (a) for PT test (*cf.*[24]), simply 0.1 ml. of patient's plasma (*pp*); (b) for prothrombin assay (*cf.*[25]), 0.1 ml. 1:10 *pp* (sal. dil.) plus 0.1 ml. proconvertin[19]-enriched beef $BaSO_4$ plasma; (c) for proconvertin assay (*cf.*[26]), 0.1 ml. 1:10 *pp* plus "asbestos-filtered" beef plasma; (d) for proaccelerin assay (*cf.*[27]), 0.1 ml. 1:10 $BaSO_4$-*pp* plus "aged" human normal plasma. The principle is that each substrate supplies all the necessary clotting factors except the one being assayed.

"Normal" standards, reference (dilution) curves, and reagent checks for these and other tests involve much meticulous experimentation. They permit assays in terms of "per cent" of normal, in each case, whether a reference curve is used or a statistical norm for an empirical (e.g., 2-stage prothrombin) unitage. A known normal is assayed with each group of tests to orient the standard to any change of reagents or test conditions.

$BaSO_4$ adsorption, of plasma, serum, or fibrinogen solutions, is effected by mixing with powdered $BaSO_4$ (Merck's), 0.1 gm. per ml., for 10 minutes at 37° C. and centrifuging off the sediment. This sediment may be eluted with ¼ vol. of 0.2 M sod. citrate for a *new specific 2-stage prothrombin assay* (Method III). First, incubate 0.1 ml. eluate with 3.7 ml. saline (0.85% NaCl), 1 ml. imidazole buffer (pH 7.3), 0.1 ml. accelerin ($BaCO_3$-adsorbed beef serum,[28] 1:8 dil.), 0.1 ml. beef proconvertin (*cf.*[19]), 0.5 ml. "soluplastin," 0.5 ml. 0.15 M $CaCl_2$. Secondly, time the clotting, at 28° C., of 0.2 ml. fibrinogen with 0.2 ml. samples of incubate at successive minute intervals. Clotting times are referred to a standard normal eluate dilution curve to assay prothrombin as "percentage" (of normal). Like the orthodox 2-stage (Method II), the new test activates the prothrombin (but in the fibrinogen-free eluate) to thrombin, which is then measured by the shortest clotting-time for a standard fibrinogen. The end-point is usually reached within 5 minutes and is typically stable (unlike II), indicating absence of thrombin-inactivating inhibitors. Other differences from the orthodox two-stage are non-use of acacia, employment of a fixed dilution, and a different mode of computation.

The orthodox 2-stage (Method II) for specific prothrombin assay. Defibrination of plasma is effected by collecting fibrin on a glass rod for 15 minutes after adding 0.1 ml. thrombin to 0.5 ml. plasma plus 0.4 ml. saline. The bovine thrombin of the Upjohn Co., supplied through the courtesy of Dr. J. T. Correll, is very satisfactory when used in a strength of 20 "units" per ml. Dilution of the defibrinated plasma is (IIa) with saline, in the "original"[29] method, (IIb) with 1:150 saline dil. $BaCO_3$-adsorbed beef serum (AcG or accelerin) in the "modified"[30] method, and (IIc) with AcG plus 1:100 beef proconvertin (ProC)[19] in our "improved" method. Activation of the suitably diluted defibrinated plasma is by incubation of 0.6 ml. with 1.8 ml. of (a) Difco's "prothrombin incubation mixture," supplied through the courtesy of Dr. C. W. Christensen, or (b) our own preferred "mix" (*cf.*[25]), viz. 23 saline, 2 imidazole buffer, 8 acacia (15%, Ca-free), 12 "soluplastin," 18 $CaCl_2$ (0.1 M). At minute intervals,

* Schieffelin and Co., supplied through the courtesy of Dr. E. W. Blanchard.

0.4 ml. of incubate is tested on 0.1 ml. fibrinogen, at 28° C., until the shortest clotting time is reached. Computation and correction factors are established.[2]

Fibrinogen. A very satisfactory fibrinogen is prepared from dog plasma, after $BaSO_4$ adsorption, by precipitation at ¼ saturation with $(NH_4)_2SO_4$, redissolving in saline and dialyzing against saline containing 0.005 M sod. citrate. Armour's bovine fibrinogen (Fraction I) is serviceable if a 1–1.5% solution is adsorbed with $BaSO_4$ and then dialyzed to low citrate content. Stock solutions are stored frozen at −20° C. in 10 ml. lots, and centrifuged free of sediment on first thawing before use.

RESULTS AND INTERPRETATIONS

Parallel tests on 100 normal and over 200 hemorrhagic cases show that the results with Method IIb or IIc agree closely with those by the other two specific prothrombin methods I or III, but often diverge widely from those of the prothrombin time test. If Method II is compared with either Method I or Method III a linear correlation is shown, with a small scatter and a computed correlation coefficient of over 0.95. Figure 1 in contrast compares data of Method II and the prothrombin time test. The discrepancies are obvious and the correlation coefficient of about 0.5 is hardly significant. Independent assays of other factors show what is now well recognized, namely, that the original one-stage "prothrombin" test is subject to other variables. These include proaccelerin (Ac globulin, labile factor, factor V, etc.), proconvertin (SPCA, stable factor, factor VII, etc.), as well as the abnormal presence of certain inhibitors and, rarely, severe deficiencies of fibrinogen. Another previously reported finding is that of a normal prothrombin time test in newborn infants despite considerable deficiency of prothrombin and proconvertin.[3] Some 30 cord blood plasmas are included in Figure 1. In all these cases there was an abnormally high (100–300%) proaccelerin.

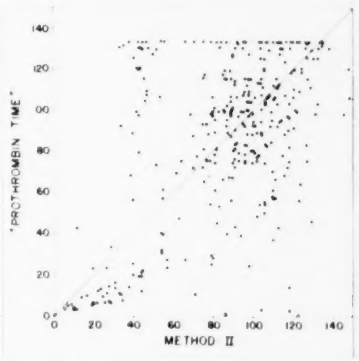

FIG. 1. Comparison of two-stage prothrombin assays (Method II) and prothrombin time tests expressed as percentages of normal.

Granting, then, that the three "specific" methods all measure the same clotting component, what is the evidence that this is indeed prothrombin? One direct answer was given by Johnson and Ferguson,[4] who used Method II to show excellent analytical recoveries of purified prothrombin added to normal human plasma.

Effects of technical variables, including those dependent on reagents. The present study confirms an earlier report[2] that Method II is very dependent upon technical variables as far as any "absolute" unitage is concerned. Clotting times are affected by temperature, pH, ionic strength and nature of salts, etc., present, and by such "fibrinoplastic" additives as the acacia. Even with this useful (if not physiological) addition, clotting times and hence unitage vary with each batch of fibrinogen. However, with one good lot of fibrinogen and the readily reproducible mixtures of the other reagents,

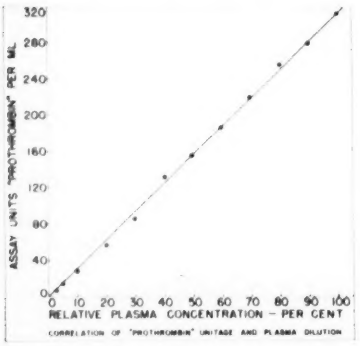

FIG. 2. Correlation of prothrombin unitage (Method II) and known plasma dilution.

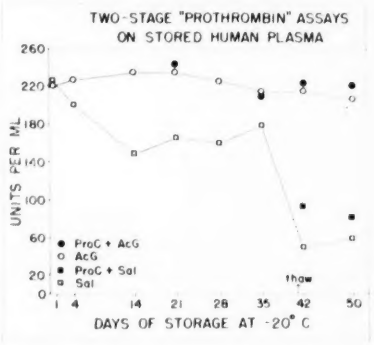

FIG. 3. Two-stage "prothrombin" assay units on normal human plasma during storage at −20° C. Diluents varied.

satisfactory agreement is observed in repeated testing of the same plasma. For instance, in 10 repeat determinations on one normal plasma the mean unitage of 385, with range 350–415, shows a standard deviation (σ) close to ± 5 per cent. Tests on 50 normal persons gave 360 (267–441, σ = 12%) with one dog fibrinogen, 30 gave 265 (200–335, σ = 11%) with another, while 70 additional cases assayed 215 (160–316, σ = 18%) with a bovine fibrinogen. Evidently, normal individuals show some variability in the 2-stage prothrombin assay, ranging ± 30-35% of the mean (100%) in our total series. However, the major determinant of the absolute unitage is the "reactivity" of the standard fibrinogen. The linear correlation (Fig. 2) between Method II unitage and known plasma dilutions (using $BaSO_4$ plasma as diluent) extends to the practical limits of the test.

Variation in the type of diluent, in step 2 of Method II, was re-studied. In the above 10 repeat determinations on a single fresh human plasma, tests made with simple saline diluent (a) gave 353 (330-398, σ = 5.7%) with the mean at 92% of that noted above with the AcG modified (b)

method. Table I shows parallel determinations on known plasma dilutions, using as diluents: (i) AcG + ProC, (ii) AcG, (iii) ProC, (iv) saline only. The fact that there was only a slight improvement on adding the accelerin and proconvertin may be attributed to the fact that these agents were already sufficient in the fresh normal plasma tested. In these and many other comparative studies the "improved" (IIc) and the "modified" (IIb) tests agreed closely, with the former usually giving a few extra units.

TABLE I. TWO-STAGE PROTHROMBIN ASSAYS ON SALINE DILUTIONS OF NORMAL HUMAN OXALATED PLASMA

Actual %	*Found values, with specified diluents* (in test):*			
strength	*(1) AcG + ProC*	*(2) AcG*	*(3) Sal + ProC*	*(4) Sal*
5	4.4	4.	3.9	3.7
10	8.4	7.6	7.6	7.8
20	18.	18.	17	18
40	36	34.	30.	31.
60	57.	54.	55.	54.
80	78.	75.	72.	79.
100	100.	100.	100.	100.
units/ml.	263	271	255	243

* Diluents, in 0.85 per cent NaCl (Sal.):
1:150 $BaCO_3$ adsorbed bovine serum (AcG)
1:100 bovine proconvertin (ProC)

Influence of plasma proaccelerin. That loss of labile proaccelerin (AcG) is the cause of unduly low 2 stage prothrombin unitage when testing aged plasmas was shown by Fahey, Ware, and Seegers.[7] Figure 3 confirms this in the case of a normal human plasma stored frozen at −20° C. in 0.5 ml. lots which were thawed and tested individually over a period of 50 days. Even this excellent cold storage did not prevent a drop in unitage by the "original" Method IIa (square symbols — saline diluent, only), although this levelled off in the second week and the precipitous drop in the sixth week was associated with a (41st day) thawing (defrosting) and refreezing, which we have frequently found to cause disappearance of proaccelerin. The "modified" 2 stage (open circles) shows very satisfactory reproducibility of the true prothrombin unitage. The "improved" method (dark symbols) gives only small increases in unitage, which agrees with the currently accepted fact that proconvertin, like prothrombin, survives well in preserved plasma and a normal specimen does not need additional ProC in the test diluent.

Data on D. H. (Table 2), a clinical case of *congenital hypoproaccelerinemia* (proaccelerin assays: 0),[18] the disease originally called "parahemophilia" by Owren,[17] showed a false low prothrombin value of 47 units with saline diluent, but 310 units (117% of normal) with the AcG-modified test. However, the optimal activation time was reduced only from 5 to 3 minutes. Proconvertin addition did not significantly change these figures. D. H.'s plasma proconvertin assayed 98% (of normal).

Acquired hypoproaccelerinemias have occurred in a number of our clinical cases, with associations that include liver diseases, tromexan therapy, etc. They also require the "modified" or "improved" 2-stage for assay of true prothrombin unitage.

Influence of plasma proconvertin. The stability of proconvertin, as shown in Figure 3 (interpreted above), precludes attempts to ascertain its rôle in the 2-stage assay except on plasmas with markedly lowered proconvertin levels. Such are available in cases of *congenital hypoproconvertinemia* originally described as SPCA deficiency by Alexander *et al.*[1] in 1950. In that year we[2] reported two cases (M. T. and R. D., *correction:* R. S.) as congenital hypoprothrombinemics unresponsive to vitamin K_1 oxide. Our reappraisal in 1953[6] was based on the following additional tests: M. T., a 14-year-old white girl died in 1950, but we kept some of her frozen plasma and three years later were able to prove its normal prothrombin (but absence of proconvertin). This required our specific tests, however. Thus, the usual AcG "modified" 2-stage gave prothrombin as 34% (of normal), whereas our "improved" (ProC + AcG) method raised this to 85%, acceptably "normal" on a three-year-old plasma specimen. Moreover, the new test required a normal 4 minutes, instead of the other's 10 minutes for optimal activation. R. S., a 32-year-old white male, returned for another study in 1953 and also gave specific proconvertin assay of zero and the following variants of the 2-stage prothrombin assay, made on a 3-day-old plasma specimen (kept at −20° C.): (i) with saline diluent, 33%, after 37 minutes (!) activation; (ii) with AcG, 87%, after 10 minutes activation; (iii) with ProC (and saline), 79%, after 16 minutes activation; (iv) with ProC plus AcG, 103% in a normal 3 minutes activation.

Clearly these two cases (included in Table 2) are *congenital hypoproconvertinemics*, with essentially normal levels of prothrombin. Both gave very long "prothrombin time" tests (2% of normal) and could not have been diagnosed without the use of proconvertin.

The *acquired hypoproconvertinemia* cases in our series are almost invariably accompanied by hypoprothrombinemia and some associations are (a) normal infancy (newborn cord bloods),[19] (b) liver disease, (c) vitamin K

TABLE 2. TWO-STAGE PROTHROMBIN ASSAYS OF PLASMA (expressed as *percentage* of normal) AND PROTHROMBIN CONSUMPTION (percentage loss in serum after 1 hour at 37° C.) IN REPRESENTATIVE CASES OF HEMORRHAGIC DISORDERS. Method Hb ("modified"); Hc ("improved"); in cases marked with asterisk.

Case	*Type of disorder*	*Plasma prothr.*	*Prothrombin consumption*
L. F.	Normal (control)	100	98 (c. 90)
D. H.	Congenital hypoproaccelerinemia	117	40
M. T.	Congenital hypoproconvertinemia	85*	79*
R. S.	" "	103* (70)	60* (67)
32 new-born‡	Low proconvertin, high proaccelerin Low PTC	43 (mean) (30–59)	83 (mean) (55–95)
G. M.	Hemophilia (AHG lack); mild	117	33
J. K.	" : mild	82	62
W. B.	" : severe	107	0
R. L. (1)	PTC deficiency (no inhibitor)	85	19
Q. C.	"	100	0
	PTA-deficiency	76	low*
W. C.	Hemophilia + inhibitor (anti-AHG)	75	0
R. L. (2)	PTC deficiency + inhibitor (anti-PTC)	83	0
L. T.	"idiopathic" circulating anticoagulant	70	0
	Platelet and Vascular Disorders (platelets c. 10⁵)		
V. Y.	Acquired thrombocytopenia (10)	114	47
A. B. (1)	Familial thrombocytopenia (38)	111	70
A. B. (2)	" post-splenectomy (320)	106	95
S. C.	Thrombopathic purpura (238)	90	95
N. P.	Thrombopathic purpura (230)	89	95
R. G.	Thrombocytosis (c. 2,000)	88	97
J. W.	Schönlein-Henoch's purpura (322)	77	95
D. Q.	"Pseudohemophilia" (376)	100	95
Z. M.	Hereditary telangiectasia (298)	95	97
W. M.	Survey (452)	122	95
D. B.	Congenital afibrinogenemia	120	98
N. P.	Severe liver disease; hypofibrinogenemia, hypoproaccelerinemia, active fibrinolysin	95	0

‡ Cord bloods.

deficiency (infants), (d) cases on dicumarol or tromexan therapy. The course of these cases can be followed either with the specific methods or with the prothrombin time test. In all of them the hypoproconvertinemia is moderate and our "improved" Method II prothrombin assay does not show significant differences from the ordinary "modified" 2-stage. Figure 4 shows the results of these two variants of the prothrombin assay, (a) open circles: AcG-saline; (b) open squares: ProC + AcG diluent, and compares them with (c) the "prothrombin time" determinations: solid circles, in a

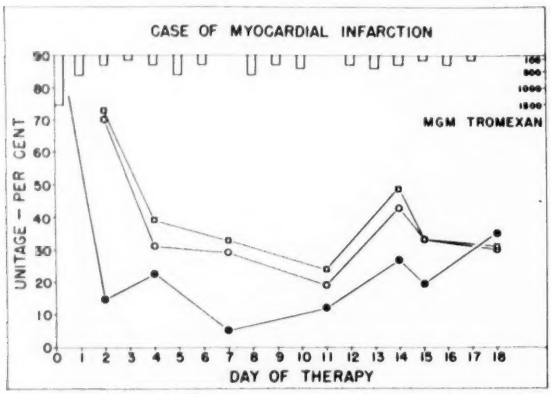

FIG. 4. Prothrombin time tests (dark circles), "modified" (open circles) and "improved" (open squares) two-stage prothrombin assays during course of tromexan therapy in a case of myocardial infarction.

case under tromexan therapy. The much lower values in (c) (cf.[11]) indicate this test's sensitivity to lowering of proconvertin as well as of prothrombin.

We have not encountered any case of genuine *congenital hypoprothrombinemia*, and the existence of such a state has even been questioned.[3]

The "improved" and "modified" 2-stage prothrombin methods have been found equally reliable on all other types of bleeding disorders. The latter method was used in the selected cases of Table 2, but in the two cases of hypoproconvertinemia (see above), corrected values (marked with asterisks) were by the "improved" method. This table also illustrates another use of the 2-stage method, namely, in estimating prothrombin consumption, although for this test the simplicity of our 1-stage (Method I) is to be preferred. High serum prothrombin values, indicating defective prothrombin consumption, are noted in hemophilia (AHF deficiency)[9] or hemophilia-like disorders, viz., PTC-deficiency,[10] PTA-deficiency,[20] and "4th. (D)

factor"[3] lack. Table 2 shows the normal plasma but abnormal serum prothrombin levels in typical cases of three of these diseases. A hemophiliac (W.C.) and a PTC-deficient patient (for several months, R. J.) showed circulating inhibitors following transfusion therapy,[17] but these did not significantly interfere with the prothrombin determinations. Another ("idiopathic") case (L.T.) with circulating anticoagulant gave a somewhat low plasma prothrombin assay. Their prothrombin time tests were fairly normal, however.

Heparin is a natural (but probably pathological) anticoagulant, which the originators[18] of the 2-stage prothrombin method considered to interfere

TABLE 3. INFLUENCE OF THROMBIN STRENGTH* AND OF HEPARIN† ON UNITAGE OBTAINED IN TWO-STAGE PROTHROMBIN ASSAY: HUMAN PLASMA

	Sal.	*Hep.†*	*Hep.†*	*Sal.*	*Hep.†*	*Sal.*
Thrombin strength*	10	10	3	2	2	0.5
Defibrination C. T. (sec.)	7.8"	9.2"	60"	19.4"	tr.	78"
Unitage, per ml. plasma	234	268	321	325	265	291

* Thrombin strength: Units per ml. of plasma mixture.
† Heparin = 0.1 units (0.001 mg.) per ml. of plasma.

with the test. Johnson and Ferguson[17] confirmed this experimentally, with excessive amounts of heparin, but found that smaller amounts (equivalent to plasma levels in heparin anticoagulant therapy) caused an inexplicable increase in the 2-stage prothrombin unitage. Table 3 presents some recent tests which confirm this last point and also offer an explanation. Normal human plasma was heparinized to 0.1 Toronto unit (1 microgram) per ml. In parallel tests, with and without heparin, the strength of thrombin used in the defibrination was also varied. The finding of an anomalous elevation in the prothrombin unitage occurred in the heparinized samples only when the thrombin was unduly strong. It never exceeded the unitage with optimal strength thrombin (without heparin). It is suggested that there is an optimal strength for the thrombin used in the defibrination step of the assay. When the thrombin is too strong, a little heparin (which, with plasma cofactor, is inhibitory to thrombin) can correct this.

Radiation sickness. An addition to the literature[7] on the subject of radiation hemorrhage is the human case (R. T.) presented in Table 4. This elderly male had liver carcinoma metastasizing from a primary site in the colon and was under treatment with radiogold (Au^{198}) at the Oak Ridge

Hospital (ORINS) when we made the cited tests, reproduced (with permission) in Table 4. The studies made on the day before the Au^{198} injection showed a normal plasma prothrombin but deficient prothrombin consumption. Residual (1 hour) serum percentage is stated. By the 4th day, prothrombin consumption was back to normal and remained so until the 19th day, becoming increasingly defective until the 22d day; the patient died next day from a massive hemorrhage at the primary carcinoma site. Plasma prothrombin levels fluctuated but were abnormally low only terminally. The last two observations of diminished prothrombin consumption

TABLE 4. PROTHROMBIN CONSUMPTION TESTS (TWO-STAGE) ON CASE OF LIVER CARCINOMA (METASTASIS) TREATED WITH RADIO-GOLD (Au^{198})

Day of therapy	*1*	*4*	*8*	*13*	*19*	*22*
Plasma pro. (u./ml.)	510	470	313	340	445	184
Serum, 1 hour Resid. pro. (%)	23	1	2	2	20	45
Platelets x 10^3	243	280	235	420	158	43

could be correlated with developing thrombocytopenia, but platelet counts were normal in the earlier tests.

Thrombocytopenias are typically accompanied by normal plasma prothrombin levels, but deficiency of prothrombin consumption.[7] In Table 2, Case V. Y., with a platelet count of 10,000 per mm.,[3] is typical, and case A. B. shows recovery after splenectomy.

We have quantitative tests for platelet functions, viz., (a) thromboplastin, (b) accelerator factor, (c) clot retractor factor, and (d) vasoconstrictor factor (5 hydroxytryptamine). Cases with normal numbers of platelets may be functionally deficient ("thrombocytopathia"), and in Table 1, S. C. lacked (a) and (b) and N. P. lacked the retractor factor. However, both showed normal prothrombin levels and normal prothrombin consumption. This is the case also when platelets are in excessive numbers, e.g., >2,000,000 per mm.,[3] in case R. G. (an atypical leukemia). The other (vascular, etc.) types of purpuras illustrated give normal platelet and prothrombin tests. Prothrombin tests (with fibrinogen added) are normal in *congenital afibrinogenemia* (D. B.)[6] *Acquired hypofibrinogenemia*, e.g., in severe liver disease, is usually accompanied by severe hypoprothrombinemia, often hypoproconvertinemia, and other clotting factor anomalies. Case N. P. was unusual in showing normal plasma prothrombin, but absence of prothrombin consumption. A complete analysis of this case

would require tests beyond the scope of the present investigation. The significant factor may be the active fibrinolysin, destroying proaccelerin as well as fibrinogen, the prothrombin and plasmatic thromboplastic factors being resistant.

CONCLUSIONS

Technical study and clinical laboratory use attest the value of the two-stage assay as a true measure of prothrombin in plasma and in serum. The test must be "modified" to ensure adequacy of (pro)accelerin and, in severe deficiencies, of (pro)convertin also. Clinical applications here illustrated include (i) differential diagnosis of genuine hypoprothrombinemias (even in "mixed" deficiencies) from cases lacking the "accessory" factors, namely, proconvertin or proaccelerin; (ii) the following of the course of prothrombin levels in disease and after giving "hypoprothrombinemic" (dicumarol, tromexan, etc.) drugs and vitamin K; (iii) also, the following of prothrombin levels in infancy; (iv) the establishing of the essential normality of the plasma prothrombin level in afibrinogenemia (congenital), hypoproaceleriemia ("parahemophilia"), hypoproconvertinemia (SPCA deficiency), hemophilia, PTC[1] and PTA[2], etc.[3] deficiencies, thrombocytosis, thrombocytopenia, thrombocytopathias, vascular purpuras, and radiation sickness (except terminally). Heparin and perhaps certain other pathological inhibitors of clotting may present some technical problems in these tests. The prothrombin time test is affected by some factors other than prothrombin but is valuable if this does not confuse the issue. The prothrombin consumption test is another application of "specific" prothrombin assay methods. The list of hemorrhagic disorders accompanied by defects in prothrombin consumption has a common denominator, namely, some cause of delayed or incomplete prothrombin activation. Taken with other modern tests of the blood-clotting mechanisms, the above techniques are of significant practical value in the elucidation of many bleeding and clotting disorders.

ACKNOWLEDGMENTS

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REFERENCES

1. Aggeler, P. M., White, S. G., Glendening, M. B., Page, E. W., Leake, T. B., and Bates, G.: Plasma thromboplastin component (PTC) deficiency: a new disease resembling hemophilia. Proc. Soc. exp. Biol. (N.Y.), 1952, *79*, 692.

2. Alexander, B., Goldstein, R., Landwehr, G., and Cook, C. D.: Congenital SPCA deficiency: a hitherto unrecognized coagulation defect with hemorrhage rectified by serum and serum fractions. J. clin. Invest., 1951, *30*, 596.
3. Allen, J. G., Cronkite, E. P., Ferguson, J. H., and other discussants: *Irradiation hemorrhage*. Fifth Conference on Blood Clotting and Allied Problems. New York, Trans. Josiah Macy, Jr. Foundation, 1952.
4. Biggs, R. and MacFarlane, R. G.: *Human blood coagulation and its disorders*. Springfield, Ill., Charles C Thomas, 1953, 406 pp.
5. Boyles, P. W., Ferguson, J. H., and Muehlke, P. H.: Mechanisms involved in fibrin formation. J. gen. Physiol., 1951, *34*, 493.
6. Brinkhous, K. M.: A study of the clotting defect in hemophilia: the delayed formation of thrombin. Amer. J. med. Sci., 1939, *198*, 509.
7. Brinkhous, K. M.: Clotting defect in hemophilia: deficiency in a plasma factor required for platelet utilization. Proc. Soc. exp. Biol. (N.Y.), 1947, *66*, 117.
8. Fahey, J. L., Ware, A. G., and Seegers, W. H.: Stability of prothrombin and Ac-globulin in stored human plasma as influenced by conditions of storage. Am. J. Physiol., 1948, *154*, 122.
9. Ferguson, J. H. and Lewis, J. H.: *Congenital hypoprothrombinemia*: Discussion, pp. 35-38. Third Conference on Blood Clotting and Allied Problems. New York, Trans. Josiah Macy, Jr. Foundation, 1950.
10. Fresh, J. W., Ferguson, J. H., and Lewis, J. H.: Blood clotting studies in parturient women and the newborn. Obstet. Gyn., (in press).
11. Hurn, M., Barker, N. W., and Mann, F. D.: Variations in prothrombin and antithrombin following the administration of dicumarol. Amer. J. clin. Path., 1947, *17*, 712.
12. Johnson, C. L., Jr. and Ferguson, J. H.: Some factors concerned with the two-stage plasma prothrombin assay. J. Lab. clin. Med., 1951, *37*, 294.
13. Lewis, J. H. and Ferguson, J. H.: Partial purification of human prothrombin and proconvertin: their characteristics and interaction. J. clin. Invest., 1953, *32*, 915.
14. Lewis, J. H. and Ferguson, J. H.: Hemorrhagic diathesis due to PTC (plasma thromboplastin component) deficiency. Proc. Soc. exp. Biol. (N.Y.), 1953, *82*, 445.
15. Lewis, J. H. and Ferguson, J. H.: Afibrinogenemia: report of a case. Amer. J. Dis. Child., 1954, *88*, 711.
16. Lewis, J. H. and Ferguson, J. H.: Hypoproaccelerinemia. Blood, 1955, *10*, 351.
17. Lewis, J. H., Ferguson, J. H., and Arends, T.: Hemorrhagic disease with circulating inhibitors of blood clotting: anti-AHF and anti-PTC in eight cases. Blood (in press).
18. Lewis, J. H., Fresh, J. W. and Ferguson, J. H.: Congenital hypoproconvertinemia. Proc. Soc. Exp. Biol. (N.Y.), 1953, *84*, 651.
19. Owren, P. A.: Parahaemophilia: haemorrhagic diathesis due to absence of a previously unknown clotting factor. Lancet, 1947, *1*, 446.
20. Owren, P. A.: Prothrombin and accessory factors. Amer. J. Med., 1953, *11*, 201.
21. Quick, A. J., Stanley-Brown, M., and Bancroft, F. W.: A study of the coagulation defect in hemophilia and in jaundice. Amer. J. med. Sci., 1935, *190*, 501.
22. Quick, A. J. and Stefanini, M.: The concentration of the labile factor of the prothrombin complex in human, dog, and rabbit blood: its significance in the determination of prothrombin activity. J. Lab. clin. Med., 1948, *33*, 819.
23. Rosenthal, R. L., Dreskin, O. H., and Rosenthal, N.: New hemophilia-like disease caused by deficiency of a third plasma thromboplastin factor. Proc. Soc. exp. Biol. (N.Y.), 1953, *82*, 171.
24. Spaet, T. H., Aggeler, P. M., and Kinsell, B. G.: A possible fourth thromboplastic component. J. clin. Invest., 1954, *33*, 1095.
25. Ware, A. G. and Seegers, W. H.: Two-stage procedure for the quantitative determination of prothrombin concentration. Amer. J. clin. Path., 1949, *19*, 471.
26. Warner, E. D., Brinkhous, K. M., and Smith, H. P.: A quantitative study on blood clotting: prothrombin fluctuations under experimental conditions. Amer. J. Physiol., 1936, *114*, 667.

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TEMPORAL LOBE SUPPRESSOR CORTEX IN MAN‡

Dusser de Barenne and McCulloch[1] demonstrated that activation of certain parts of the cerebral cortex produces a suppressor response characterized by decreased electrical activity of all areas of the cerebral cortex manifested by decrease in the motor responses and evoked potential responses of the appropriate cortex. The first of these areas described was area 4 S.

They subsequently demonstrated[2] other suppressor areas: 8 S, 19 S, and 2 S. These areas were shown by neuronography to discharge into the caudate nucleus[3] and to have an inhibitory function on this structure. Dusser de Barenne and McCulloch conjectured a cortico caudate thalamo cortical circuit which served as a dampening circuit on the activity of other areas of the cortex. In 1944 Garol and Bucy[4] demonstrated to their satisfaction that the suppression of motor response could be evoked in man by electrical stimulation of a circumscribed area of the human cerebral cortex. This area was equivalent to area 4 S as had been previously described in infrahuman primates.

Some investigators in the neurological field have not been convinced that the suppressor areas exist. Some believe that the response obtained is due to drying of the cortex and is not really a function of the cerebral cortex, holding that it is akin to the spreading depression described by Leao.[5] Some neurosurgeons who are also competent neurophysiologists have failed to demonstrate the suppressor area in humans at operation, while other neurosurgeons, in the same category, feel that they may have, from time to time, elicited points of suppression.

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‡ One of the authors of this paper (F. M. F.) had the great privilege of spending the year 1940-1941 in the laboratory of Dr. John F. Fulton as a research fellow under the aegis of the Rockefeller Foundation. This was an invaluable year in training, education, and research, and also in the understanding of the role of the medical school in the total university. The atmosphere of Dr. Fulton's department afforded the Fellow a contact with those from other laboratories, and it was possible to observe at first hand the Dusser de Barenne and McCulloch studies of the suppression phenomenon.

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The present authors hold that the experiments of Dusser de Barenne and McCulloch are valid. We feel that most of the investigators who disagree did not actually repeat the experiments with the same techniques and the same patients as the original investigators.

The important point, so often overlooked by subsequent investigators, is that Dusser de Barenne and McCulloch described a period of from one to three minutes after the application of strychnine to the suppressor regions before the strychnine firing appeared, and then a lag of three to eight minutes before the suppression is seen in the other areas of cortex. Moreover, the suppression is not uniform over the entire cerebrum at one time, and indeed there is often a waxing and waning of suppression.

As seen in the original map of Dusser de Barenne and McCulloch, area 4-S stands in relationship with motor cortex; area 8-S might be considered in relation with prefrontal cortex as well as premotor; area 2-S is a part of the sensory cortex; and 19-S, the visual cortex. Area 24 on the medial surface of the hemisphere is a part of the cingulate and limbic cortex and thereby brings suppressor function into the field of what we may call affective cortex. Their map, however, included no suppressor area in the temporal lobe in relationship to auditory cortex. It seemed, therefore, that there was a conspicuous gap in the suppressor areas as mapped up to that time. This presented a challenge, especially in view of the present-day interest in temporal lobe epilepsy.

This led to the search for a suppressor area in the temporal lobe of the infrahuman primate. In a series of studies carried out on twenty-one *Macaca mulatta* monkeys, we located a temporal lobe suppressor area.[1] This area is in the first temporal convolution at the base of the Rolandic fissure. In a second series of monkeys the temporal suppressor area was located and treated so as to produce chronic, experimental epilepsy.[2] The seizures produced from the temporal suppressor area of the *macaque* are inhibitory in type. The monkey becomes listless, loses muscle tone, has no defensive reflexes, and, for example, it is possible manually to empty the food pouches without danger or difficulty. These attacks usually last about three minutes, and at the end of that time the monkey is frequently more active than normal for thirty seconds or so, then returns to his normal state.

We were, therefore, convinced that suppressor cortex does exist, that there is a suppressor cortex in the temporal lobe of the *macaque*, and that chronic seizures can be produced from this suppressor area. The next question was, is there a temporal lobe suppressor area in man and, if so, can this area play a part in seizure manifestations? At this point we were very fortunate in the course of an exploration of the temporal lobe in a patient with psychomotor seizures to discover the temporal suppressor region.

Case report. The patient, R. B., is a 27-year-old white male who was admitted to Georgetown University Hospital on March 12, 1954, complaining of epileptiform seizures. The patient had a series of febrile convulsions in childhood and was well after this until age 14 when he began to have his first psychomotor seizures. These consisted of periods of stopping, staring, and mumbling to himself. They would last from one to

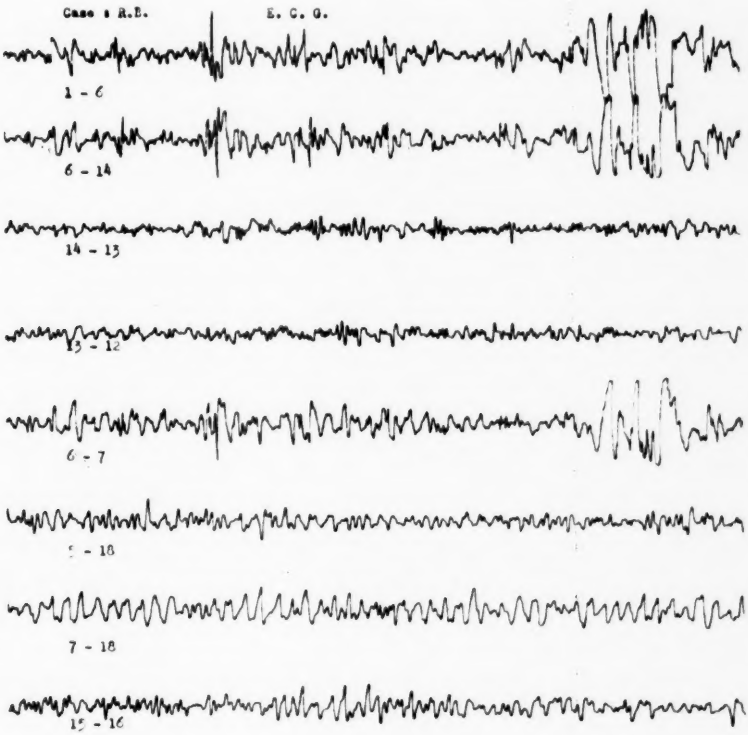

FIG. 1. (Case R. B.) E.C.G. tracings at operation show spiking discharges at electrode 6.

two minutes, and after this, he would be drowsy. He has had only one major convulsion since adulthood, and this was in 1949. The psychomotor seizures, however, occurred at a frequency of one to three per month. During the psychomotor seizures he sometimes merely stood and stared. The patient works in the family textile factory, and the attacks were evidenced by cessation of activity when he was stacking materials, conversing on the telephone, or computing figures. There was a lapse of consciousness lasting usually between one and three minutes. These seemed almost like petit mal absences; however, on rare occasions, he would mumble and make some irrelevant

statement, such as, "What are we doing?" and for this he had total amnesia. On a few occasions he has carried on motor activity such as stacking materials in the wrong place, or he has mixed the manufactured products which he was sorting for sizes.

Adequate medication with phenobarbital, Dilantin, Mesantoin, Milontin, and Mysoline all failed to effect a permanent freedom from seizures. Each new medication for a time caused a transient decrease in spells, but they soon recurred at the usual frequency of several per month.

Past history. The family history is negative for epilepsy. His birth and development were normal. He is the second in birth order. There have been no undue illnesses except that he had whooping cough at the age of two, and it was during this episode that he had his first convulsive seizure.

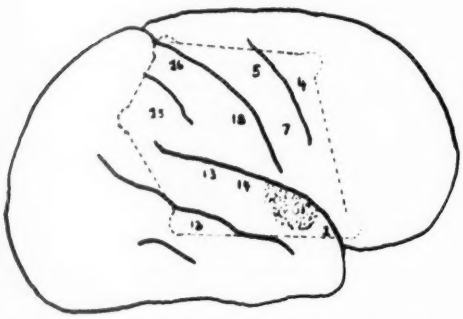

FIG. 2. (Case R. B.) The size of the bone flap is indicated by a broken line. The placement of the electrodes over the exposed cortex is indicated by numerals. The stippled area around electrode 6, site of spiking focus, was removed at operation.

Physical examination revealed a well-developed, well-nourished male. The general physical examination was entirely normal. The neurological examination was also normal.

The usual laboratory studies on blood and urine were all normal. Blood serology and sugar were normal. Skull films were normal. The spinal fluid examination was clear and colorless with an opening pressure of 120. It contained 1 lymph/mm^3 and 50 mg % of total protein. Colloidal gold sol was 0011110000. Spinal fluid serology was negative.

Twenty electroencephalograms have been performed over the past five years. Four records presented no abnormality, while in the other sixteen there was a right temporal focus with spiking discharges. The focus was also evidenced in the readings from the right ear electrode. The pneumoencephalogram showed no disproportion between the ventricles, and there was no displacement of the ventricular system. In view of the persistent electroencephalographic focus, the definite psychomotor type of seizure, and the failure of anticonvulsant medication, it was deemed advisable that the patient undergo surgical intervention. On March 31, 1954, the lateral surface of his cerebral hemisphere was exposed, electrodes were placed in a scattered fasion over temporal, parietal, and frontal lobes. There was no abnormal electrical activity except electrode No. 6 (Fig. 1). This was on the first temporal convolution near the base of the Rolandic fissure (Fig. 2). This area was stimulated electrically; electrical stimulation at 4 volts,

50 cycles at region of electrode No. 6 produced a period of suppression of electrical activity which lasted some twenty minutes (Fig. 3). No apparent change in the state of consciousness was evident to the anesthesiologist during this stimulation. The patient was asked to count, and this region was again stimulated electrically. This caused the immediate cessation of counting. The patient made a grunting, guttural noise about twice the duration of time he usually requires to say two digits, and immediately upon cessation

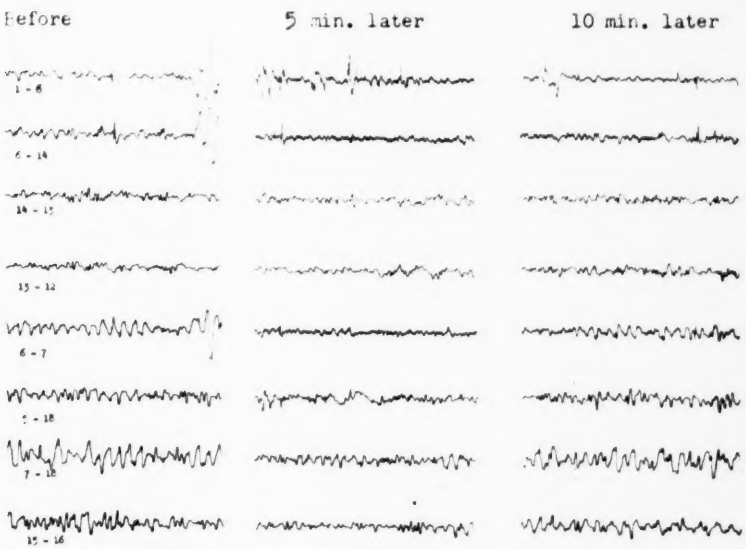

FIG. 3. (Case R. B.) E.C.G. before and after stimulation (using 4 V., 5 sec. and 50 cycles) at electrode 6, or temporal suppressor area. Note decrease in activity five minutes after stimulation with considerable return of activity ten minutes after.

of stimulation, the guttural noise stopped. He then took up the last previously mentioned number. We were interested in seeing whether induction of sleep would alter the activity of this area, and he was given 5 ml. of 2½% solution of Pentothal rather rapidly; there was immediate rapid firing activity of high voltage spikes beginning about 4 to 6 per second and building quickly to 20 to 25 per second. These sometimes lasted from three to four minutes. This response to Pentothal occurred on three separate trials scattered over a period of about an hour (Fig. 4).

The electrodes were moved to cover different areas of the exposed cortex and Pentothal was found to produce the abnormal discharge only from the

region of this one electrode. This area was excised, and after the excision no further electrical abnormalities could be detected. The removal was by subpial suction. Neither electrical stimulation nor Pentothal produced further discharges from this area.

CONCLUSIONS

It is apparent that there is a suppressor area in the temporal cortex of the higher primates and that this can be shown in man as previously has

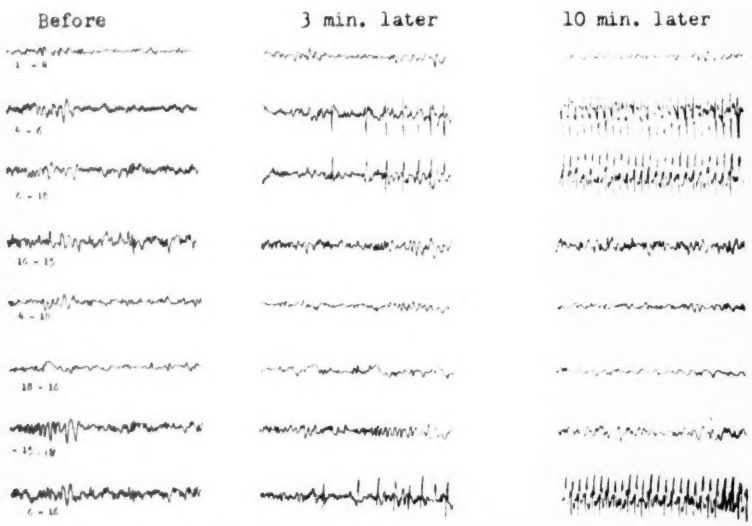

FIG. 4. (Case R. B.) E.C.G. before and after Pentothal activation of the seizure focus.

been shown in regard to area 4 S. We believe that we have now demonstrated a suppressor area in the temporal lobe, not only in the *Macaca mulatta*, but also in man. The seizures can be elicited from this area in the monkey by electrical stimulation in the awake state and by the production of chronic experimental epilepsy. In man, in at least an occasional case such as ours, the temporal suppressor area may be the site of the epileptogenic focus.

While no definite clinical seizure was apparent as a result of electrical stimulation, we still wondered whether there might not be some activity that was escaping our notice and hence the introduction of the counting technique to see whether there was a transient disturbance of consciousness

The responses of the patient with the cessation of counting, the guttural noise (for which he subsequently had amnesia), all indicated that this was also a matter of suppression. We do not feel that this could be a simple inhibition of speech, although from the single experiment we have at hand, we do not feel that we can draw any firm conclusion on this point.

The possible rôle of suppressor cortex in psychomotor seizures certainly presents a stimulating and interesting challenge. It would undoubtedly be foolhardy to claim or to concede that all psychomotor seizures originate in suppressor cortex, even though so many psychomotor seizures have their onset in what might be called a psychomotor absence. An occasional patient such as ours will have psychomotor absences as his predominant seizure type, and this is indeed difficult to differentiate from petit mal epilepsy on one hand, or, when it occurs in pure culture in older patients, from other nonepileptogenic manifestations.

The ease with which the temporal suppressor region was found in this patient is explained on the basis that this region was firing spontaneously and was located in a region corresponding to that in our *Macaca mulatta* studies. The spontaneous firing called attention immediately to the area, and there was no need for a laborious search.

The temporal suppressor area may not in itself be the primary firing area in cases of psychomotor epilepsy, but may, by its activation during the spread of the seizure discharge in the temporal lobe, ultimately bring its full force to bear in the seizure pattern.

The electrical seizure derived from this region by Pentothal injection raises many questions. At this time there is no answer to these questions. Certainly, our monkeys have not yielded the same response to Pentothal injections.

SUMMARY

In addition to the previously described regions of the suppressor cortex, there is a suppressor region of the temporal lobe which is in the superior temporal convolution near the base of the Rolandic fissure and which could be called area 42 S.

This region is present in both *Macaca mulatta* and in man. In *Macaca mulatta* stimulation of this area produces acute seizures and decreased activity which we prefer to call suppressor seizures.

By appropriate methods of producing chronic epilepsy, it is possible to produce spontaneous epilepsy in these monkeys, the seizure pattern being the suppressor type and the brain wave pattern showing suppression following abnormal spiking.

The suppressor area of the temporal lobe in man may play a part and, indeed, occasionally a prominent part in seizure patterns of temporal lobe patients.

REFERENCES

1. Dusser de Barenne, J. G. and McCulloch, W. S.: Suppression of motor responses upon stimulation of area 4 S of the cerebral cortex. Amer. J. Physiol., 1939, *126*, 482.
2. Dusser de Barenne, J. G., Garol, H. W., and McCulloch, W. S.: Physiological neuronography of the cortico-striatal connections. Ass. Res. nerv. ment. Dis., 1942, *21*, 246.
3. Garol, H. W. and Bucy, P. C.: Suppression of motor response in man. Arch. Neurol. Psychiat. (Chicago), 1944, *51*, 528-532.
4. Huertas, Jorge, O'Doherty, Desmond, and Forster, Francis M.: Evidence for suppression from the temporal lobe in the monkey. Arch. Neurol. Psychiat. (Chicago), 1953, *70*, 393-398.
5. Huertas, Jorge and Forster, Francis M.: Seizures elicited from the suppressor regions of the temporal lobe in monkeys. Trans. Amer. Neurol. Ass., 1954, *79*, 22-23.
6. Leao, A. A. P.: Spreading depression of activity in the cerebral cortex. J. Neurophysiol., 1944, *7*, 359-390.
7. Mettler, F. A.: Relation between pyramidal and extrapyramidal function. Res. Publ. Ass. nerv. ment. Dis., 1942, *21*, 150-227.

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THE UNDERGRADUATE ACTIVITIES OF SOME CONTRIBUTORS TO NEUROLOGICAL SCIENCE

> "For many reasons it is desirable that a medical student be conducted early in his career to the front line trenches of medical and physiological discovery. Let him realize that men as young as himself have made important contributions: that de Graaf at 23 years of age devised the first pancreatic fistula; that Helmholtz at 24 measured for the first time the heat production of frog muscle; that Johannes Müller at 25 had enunciated the principle of specific nerve energies. Let him discover that simple facts were once hidden in a fog of faulty observation and faulty reasoning, and that it was sometimes the enquiring minds of students like himself that made matters clear."
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> *John Farquhar Fulton*[a]

In no branch of medicine is John Fulton's statement more applicable than in that dealing with the nervous system. This paper attempts to bring into historical perspective the undergraduate apprenticeship of a number of neurological pioneers no longer living. In some cases the student's investigation was related to his later contributions to neurology, as in the case of Sherrington, Claude Bernard, and Pavlov. In others, such as Charcot, Romberg, and Magnus, the undergraduate thesis or contribution was in a field other than neurology.

Few students in history can have made such a momentous discovery as that by Gennari in 1776 when he saw for the first time the "white line" which characterizes the occipital cortex of the human brain. It was this finding which fired the imagination of generations of researchers seeking a specialized cortical structure to match each cortical function. The available descriptions of Gennari, chiefly by his biographer Marmo, suggest an open-handed student who shared his small bursary with the indigent and with his gambling companions. For our purposes, however, the interesting characteristic of Gennari was his curiosity about the structures which he saw as he did autopsies for the professor of pathology at Parma, Michele Girardi, a pupil of the great Morgagni.

Gennari was sufficiently observant to notice also that icicles formed within the ventricles of brains of frozen cadavers. He correctly surmised

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that the cerebrospinal fluid between the cerebral cortex and the meninges served to cushion the brain against outward shocks. Gennari's fine was discovered independently by Samuel Sommerring, that remarkable genius whose graduation thesis in medicine put forth the classification of the cranial nerves which was to displace that of Thomas Willis.

Fifty years after Gennari's discovery L. F. Bravais, in his Paris thesis,[3] described local motor convulsions, and thus a further stage in the localization of cortical function was reached. In 1836 another student, Marc Dax,[4] wrote his thesis on the occurrence of lesions of the left hemisphere in cases of aphasia. This delineation of the speech center in the left hemisphere in right-handed persons was another major milestone. Dax was an enterprising student and actively searched for a right-hemispheral lesion in a right handed aphasic. The best proof of his theory, possibly, was the fact that he was unable to find such a case.

The subject of aphasia knew no greater students than Sir Henry Head and Pierre Marie. Head began his undergraduate contributions to the neurological literature by writing a paper on the action potential of nerve.[5] From Hering's laboratory at Halle, the scene of Volkmann's unwitting discovery of the cardio-inhibitory action of the vagus, Head published, in 1889, a longer study on the respiratory effects of the vagus nerve.[6]

Marie, on the other hand, wrote his first paper in the field of endocrinology, and in his graduation thesis at the University of Paris in 1883 gave the first description of the tremor of thyrotoxicosis.[7] Similarly, the great Charcot, a pioneer in cerebral localization, wrote his graduation thesis in Paris in 1848 on "The affection described under the names of primary asthenic gout, nodosities of the joints, and the primary form of chronic articular rheumatism."

Yet another pioneer in the parcelation of cerebral function was Constantin von Economo (1876-1931) whose early interests were endocrinological. As an undergraduate medical student in Vienna he wrote a paper on the pituitary glands in birds under the guidance of von Ebner.

Even phrenology had its student contributors in the persons of Niclas and Spurzheim who assisted Gall in his studies!

The earliest use of staining procedures in the study of cerebral cytoarchitectonics was that of Rudolph Berlin. At the age of twenty five, in his graduation thesis at Erlangen,[8] Berlin described the pyramidal, spindle, and granular cells. Turning to gross anatomy we find Frederick Meckel publishing his graduation thesis in 1748 on the sphenopalatine ganglion, which he was the first to describe. We also find the student R. B. Hirsch naming the Gasserian ganglion in honor of his teacher, Johann Ludwig Gasser of Vienna, in 1765. (There are few enough instances of this in the

history of medical teaching.) The romantic Santiago Ramón y Cajal, prior to entering upon the study of medicine proper, was working on an atlas of osteology, the specimens having been procured by grave-robbing expeditions in company with his surgeon father in Spain.

Sir Victor Horsley was a prolific writer as a medical student. Even before entering medical school he was, like Osler, dissecting animals, working with the microscope, and grinding his own sections of bone for study. While a medical undergraduate, Horsley addressed the Students' Medical Society at University College, London, on his own researches. The first paper was entitled: "On the endings of the tendons in the rat's tail." The second communication, awarded a prize of £5 by the students, was "On the terminations of muscular fibres; and a note on the structure of intervertebral discs." Horsley's undergraduate activities were prodigious. He wrote on dress reform for women, provided Gowers with illustrative drawings of the relations of the spinal nerves to the vertebral column and Bastian with two plates for his book, *The brain as an organ of the mind*. Six months before graduation Horsley wrote with Bastian an important paper, "Arrest of development in the left upper limb in association with an extremely small right ascending parietal convolution." For good measure Horsley also carried on some bacteriological research with F. W. Mott. Horsley was known to his classmates as "The Germ" because of his bacteriology, "The Vulture" because he expected to get post mortems on all his cases, and "Archibald Allright" for his optimism. Horsley's crowded and brilliant student career was but a quiet prelude to a hectic, creative, and varied life as the founder of neurosurgery, and as political candidate, reformer, researcher, and soldier. As he plunged into the Great War, in which he was to die, he told his wife: "Don't worry about me, I don't matter. I can't live for ever. It's the young that matter."

In the field of histology the students Remak and Helmholtz began with the nervous system, while Kolliker and Waller made their earlier contributions in other fields. It is interesting to note that all four were contemporaries. Robert Remak (1815-1865) was a protege of the great Johannes Muller, and on the latter's suggestion investigated the finest fibers in the nervous system, which even today we refer to as "Remak's fibers." In 1836, two years before his graduation in medicine, Remak was describing these structures in Muller's *Archiv*. Again in 1837 he described his fibers in Froriep's journal. In 1838 he wrote his doctoral thesis on them. By the time Remak graduated from Berlin he had shown: (a) that the axis cylinder is the transmitting part of the nerve trunk; (b) that in vertebrates nerve fibers spring from nerve cells; (c) that there are unmyelinated fibers in the sympathetic nervous system (and he postulated that they arose from

sympathetic ganglion cells); and (d) that ganglion cells exist on the walls of the heart and in the intestines in men and the lower animals. He opened his thesis with a quotation from Francis Bacon: "Neither manual work alone nor imagination unchecked by facts is worth very much." The undergraduate contributions, important as they were, soon were overshadowed by the later discoveries of this neglected figure in the history of medicine. He was a forerunner of many of the doctrines which we take for granted today. Kolliker insisted that Remak deserved the credit for the view "omnis cellula e cellula." Remak's views on the central representation of the autonomic nervous system have a modern ring. His work on the cervical sympathetic antedates that of Horner by fourteen years. He was the first to describe correctly the villi of the intestines, pulsus paradoxus, the cell as the unit of muscle, and the true morbid histology of the lung in pneumonia.

Hermann von Helmholtz (1821-1894), in his graduation thesis of 1842, confirmed Remak's findings concerning nerve cells as the origin of nerve fibers. This he did on invertebrates. Prior to graduation Helmholtz also read a paper on venous tumors to his Army Medical School colleagues in Berlin. In the same year Albert von Kolliker (1817-1905), as a result of his investigations during the summer vacation wrote a thesis on the sexual physiology of vertebrates for the degree of Doctor of Philosophy at Zurich. He qualified in medicine a year later at Heidelberg.

Augustus Volney Waller of "Wallerian degeneration" (1816-1870) began his researches while a medical student in Paris by developing the preparation of the living frog's tongue for microscopic study of diapedesis or "Perforation of the capillaries by the corpuscles of the blood."[5] This same preparation served eventually for his great work on the degeneration of nerves peripheral to their point of section. Waller was a pioneer in many branches of neurology. He foreshadowed the vasoconstrictor role of the cervical sympathetic at the same time as did Bernard and Brown-Séquard, and in 1850 discovered the trophic influence of the retina on the optic fibers, ten years before Gudden's publication.

Student contributors in psychiatry may have been few, but they became the pillars of this branch of medicine. J. E. D. Esquirol (1772-1840), the favorite pupil of Pinel, wrote his graduation thesis in 1805 on "Les passions considérées comme causes, symptômes, et moyens curatifs de l'aliénation mental." The tide was beginning to turn in the vast sea of torture and abuse to which mental patients had been submitted. The lashing and chaining of patients and the "non injurious torture" prescribed by Reil—such as shooting off cannon and ducking patients in water—was being replaced by Pinel's humane approach. Esquirol's thesis was an attempt to clarify the role of the emotions in mental illness.

The versatile August Forel (1848-1931) was publishing papers on ants when he started medical school in Zurich in 1866 and also when he retired from his professorship in psychiatry there thirty-two years later! His life as an entomologist dates from the age of seven. His interest in psychiatry began when he fell under the spell of his teacher, von Gudden. Forel's doctoral thesis, begun in 1871 and written under the guidance of Meynert, was concerned with the mammalian optic thalamus. It is greatly to the credit of Meynert that although he disagreed with many of Forel's conclusions, he had the thesis published in the Proceedings of the Vienna Academy of Sciences.

The name of Sigmund Freud still makes the more organically inclined in neurology shudder. It might allay their fears to know that as a medical undergraduate Freud contributed some of the basic facts in neuroanatomy which we use daily. At the age of seventeen he entered the University of Vienna, not to study law, as originally planned, but medicine. From 1876 until his graduation in 1881 he worked in the Laboratory of Physiology of Ernst Brucke while continuing in the medical course. The first study set him by Brucke concerned a larval form of the early vertebrate, Petromyzon. One might speculate that this was the beginning of Freud's thinking concerning phylogeny and levels of development and of function within the nervous system.

On January 4, 1877, Brucke communicated Freud's first paper to the Vienna Academy of Science. It was entitled "Spinal ganglia and the spinal cord of Petromyzon" and was later printed, being twelve pages in length and accompanied by a color plate. In 1878 the study was elaborated into one of eighty pages and four plates. He clearly showed the derivation of unipolar, posterior root ganglion cells from bipolar, sensory cells in this species. It might be noted here that Freud was no newcomer to the field of comparative neurology, having spent the summer of 1876 with Professor Claus at the Institute of Comparative Anatomy in Vienna and at the Zoological Station at Trieste.

Freud was one of the lesser forerunners of the "neurone theory" as it came to be called in Germany. In the summers of 1879 and 1880 he worked on the nervous system of the fresh water crab and emphasized the finely neurofibrillar structure of their axones. He was impressed also by the similarity of the pattern of the nervous system in invertebrates and vertebrates. From Brucke's laboratory, also, Freud published his papers on the tracts and nuclei within the medulla oblongata. At about the same period (1880) he translated into German the book by John Stuart Mill, *The Emancipation of Women*. Freud's co workers in Brucke's laboratory had equally broad interests and published on such subjects as collateral innervation, the origin

of cell nuclei, corneal innervation, and the conception of movement and space, as well as on "the nature of the psychical process."

The field of neuropathology boasts a trio of distinguished student investigators in Schilder, von Monakow, and Nissl. Paul Schilder, disciple of Exner the physiologist and Laurenz Muller the philosopher at the University of Vienna, published his first paper on a neuropathological subject before graduating at age twenty-three.

Constantin von Monakow (1853-1930), who became a leader in the field of neurology and whose life has been so gracefully portrayed by Colin Russel,[1] was a student who fled from the wax models of neuroanatomy after attending only three lectures, to be caught in the mesmerizing web of neuropathology. As a student of psychiatry on Hitzig's wards at Zurich, he was allowed to work over the neurological specimens from the autopsy room, where in his sixth semester he started on histological studies on the brain in dementia. Interestingly enough he investigated damage to the cerebral blood vessels, the brain cells, and liver in chloroform poisoning. Hitzig, who had just discovered the electrical excitability of parts of the cerebral cortex, was so impressed with von Monakow's organizing ability as a student that he sent him on a tour of investigation and study of mental institutions. In Munich, von Monakow saw von Gudden's anatomical methods, his microtome, and his set of serial sections of the human brain. This fired his imagination, as he pictured the possibilities of applying retrograde degeneration techniques to cerebral pathways. His later discoveries bear out the thesis that a student can be stimulated to do original research, given the means.

Franz Nissl (1860-1919) made his first contribution at the age of twenty-four when, in his graduation thesis, he analyzed "The pathological changes of the nerve cells of the cerebral cortex." The work was recognized by his University in Munich with the award of a special prize. Such was his student reputation that he was taken into von Gudden's Institute and given a laboratory and assistants immediately upon graduation.

Turning now to the clinical neurologists who distinguished themselves as undergraduate researchers we find a large group indeed. William Osler (1849-1919), Canada's first neurologist, was already a prodigious worker by the time of his graduation in 1872. In 1869 he had written a delightful piece in *Hardwicke's Science Gossip* entitled "Christmas and the microscope." As an undergraduate at Toronto, Osler published in 1870 his first scientific contribution on "Canadian diatomaceae." He also experimented with rabbits, trying to infect them with the trichinae found in the cadaver he was dissecting. On transferring to McGill University, because of the clinical material available at the Montreal General Hospital, Osler became an

undergraduate pathologist in earnest. One of his earliest student post-mortems was on an interesting case of "paralysis with aphasia." He prepared the gross and microscopic pathological specimens and report on a case of mammary carcinoma. His graduation thesis on pathological anatomy was of such excellence that it was awarded a special prize by the faculty. Osler's later neurological interests were wide and included "the brain as a thinking organ," the brain of the seal, gliomas of the retina, cerebral aneurysms, tuberculous meningitis, anencephaly, frontal lobe injuries, the brains of criminals, chorea, convulsions in children, progressive muscular atrophy, tabes, Jacksonian epilepsy, and "the cerebral palsies of children."

The distinguished French neurologist and editor, Edouard Brissaud (1852-1909), wrote his graduation thesis on the contractures found in hemiplegics. He pointed out the relationship of lesions of the pons to varying degrees of the disease. His compatriot, Henri Claude (1869-1945), wrote a remarkable graduation thesis in 1897 on the effects of injecting toxins such as that of tetanus into the liver. The resulting venous thrombosis opened up a new approach to the cause of multiple sclerosis. His study also included the kidney and the nervous system. For his thesis he was awarded a gold medal by the hospitals of Paris. Claude had all the qualities of the sound internist and was interested in renal function and sodium retention, the rôle of the thymus gland in myopathies, autonomic representation in the hypothalamus, the measurement of cerebrospinal fluid pressure, and in schizophrenia. On succeeding to Charcot's chair he gave a great impetus to the development of preventive mental health services and the use of psychiatric social workers.

Another pioneer in multiple sclerosis was J. F. F. Babinski (1857-1932). His graduation thesis at the University of Paris in 1884 was a study in this disease.

In the field of hereditary diseases of the nervous system two names come to mind, Karoly Schaffer (1864-1939) and George Huntington (1850-1916). Schaffer's first paper, published while an undergraduate, was on the route of transmission of the virus in rabies. George S. Huntington, at the age of nine, was already a student of the type of chorea today associated with his name. As he made rounds with his grandfather and father in their practice in East Hampton on Long Island, New York, he recorded his impressions of the unforgettable patients afflicted with this poorly recognized illness. With the prolonged apprenticeship in medicine which this youth served *en famille* it is little wonder that he was able to write, a few months following his graduation in 1871, a paper of which Osler said, "It is truly a classic and has scarcely been improved upon since it was first set down."

It is impossible to leave the clinical neurologists without commenting upon the unusual theses of two of them. Hermann Oppenheim (1858-1919) wrote his doctoral thesis in 1881 on the metabolism of urea, a subject on which he had already published three papers. M. H. Romberg (1795-1873) gave us his classic description of achondroplasia in his doctoral dissertation in Berlin in 1817.

Finally, in the realm of neurophysiology, we see some of the most productive and original minds in the history of science. Charles Sherrington, Claude Bernard, Ivan Pavlov, and Walter B. Cannon surely were of that rank. There were others, such as Magnus, Brown-Séquard, Donders, and Raynaud, who also gave great promise in their undergraduate researches. Maurice Raynaud (1834-1881) gave the first description of the sympathetic nervous system disorder which still bears his name. This he did in his medical doctoral thesis "On local asphyxia and symmetrical gangrene of the extremities" in 1862 in Paris. Raynaud followed up his undergraduate work during the remainder of his short life of forty-seven years. He has left us, also, a delightful account of medical education in Molière's time.

Cornelius Donders, the great Dutch forerunner in the theory of evolution and in the laws of the conservation of energy, was an early contributor in the neurological field. Having completed his medical course at Utrecht too young to be graduated, he transferred to Leyden and there presented his doctoral dissertation on the pathological anatomy of the nervous system. He never strayed very far from the nervous system and made his best known contributions in ophthalmology and color vision. His papers "Muscular work and development of heat in relation to the necessary elements of food," "The influence of the vagus nerve on the cardiac movements," and "The chemical phenomena of respiration" are still of great interest. He counted among his admirers Jonathan Hutchinson and Hughlings Jackson.

The brilliant and erratic Charles Edouard Brown-Séquard (1817-1894) wrote his graduation thesis at Paris in 1846 on "Recherches et expériences sur la physiologie de la moelle épinière." Even at this stage in his career he was investigating the crossing of the sensory tracts in the spinal cord. His thesis was based on extensive work on birds, mammals, and cold-blooded vertebrates and showed that the views of Sir Charles Bell on sensory tracts in the cord were in need of modification.

The many-sided genius Rudolf Magnus (1873-1927) was a student researcher of note. His undergraduate work was not neurological, but rather concerned a method for the measuring of blood pressure in an exposed artery. He presented his early work before the International Congress of Physiology at Bern in 1895 and elaborated on this subject in his doctoral thesis upon graduating from Heidelberg in 1898.

Pavlov's very full life as an investigator in neurophysiology began in the Veterinary Institute of the University of St. Petersburg. His first work was on the nerves to the pancreas and his second on the production of a permanent pancreatic fistula. He carried this forward while a summer student in Heidenhain's laboratory in Breslau in 1877 and published his results in 1878. The outstanding Russian clinician, S. P. Botkin, organized a little laboratory for clinical research and placed Pavlov in charge of it even before his graduation in medicine. Pavlov's biographer, Boris Babkin, has written: "This is in truth an amazing fact—that a recently graduated science student, who had not yet finished his medical course and who himself should have been studying under another, became the director of scientific investigations in the most famous clinic of internal diseases in Russia."[1]

Like Pavlov, Claude Bernard began and ended his long research career with investigations on the neurophysiology of the digestive system. While a medical student on the wards he saw a case of facial paralysis. This stimulated him to investigate the distribution and function of the chorda tympani, a subject to which he returned over and over again throughout his life. His doctoral thesis, published in Paris in 1843, described the secretion and rôle of the gastric juice. It was this work which almost brought Bernard's career as an investigator to a close, for one of the dogs, in which he had placed a gastric cannula, escaped and returned to its owner—the local commissioner of police. It is a tribute to the talents of Bernard that he was able to pacify the official, who thereupon became his chief benefactor and animal supplier!

Walter Bradford Cannon was riding in a Boston train one auspicious day early in 1896 when he heard a man say, "They have made a new invention by which they can look right through people." Within a day Cannon, a first-year student in medicine, was at the door of Professor Bowditch asking if he might experiment with Rontgen's new waves in a study of swallowing and digestion. By December of the same year Cannon was able to demonstrate to members of the American Physiological Society the gastric motility of animals fed with bismuth subnitrate. Eventually he came upon a cat of a special kind. It was so angered by the proceedings that all gastro-intestinal movements had ceased. This was the critical case which turned Cannon into his best-known field of endeavor, that of bodily changes in pain, hunger, fear, and rage. His voluminous works on the autonomic nervous system established the mechanisms which regulate Claude Bernard's "milieu interieur."

Finally we come to "the philosopher of the nervous system," Sir Charles Sherrington (1857-1952). It has been truly said that as Harvey was to the circulatory system so was Sherrington to the nervous system. His long life

of ninety-five years spans so much of the modern history of neurology — including almost all of neurophysiology — that it is impossible in this paper to encompass much of it. His earliest writings concerned structure and function in the nervous system of a dog demonstrated by Goltz at the International Medical Congress in London in 1881. While still a medical undergraduate at Cambridge, Sherrington wrote two papers on this interesting subject with the assistance of J. N. Langley.

The methodical analysis of the complexities of the nervous system which characterized all of Sherrington's work is evident even in these undergraduate writings. It is too rarely appreciated that Sherrington was not only a physiologist, he was an expert histologist, anatomist, and pathologist as well. He served as a Demonstrator in Anatomy while a student at St. Thomas' Hospital Medical School in 1883. His histological preparations are not well known because they were often deleted from his papers by editors of physiological journals. It was Sherrington's grasp of neurohistology which enabled him to fathom Ramón y Cajal's early papers. It was also his facility in Spanish, learned on a cholera research expedition to Spain in 1885, which saved some of Cajal's efforts from oblivion. That isolated and locally ridiculed prophet distributed his early reprints to the crowned heads of Europe in an effort to have Spanish science recognized. It was Sherrington, as Secretary of the Royal Society, who brought Cajal to London in 1894 to give the Croonian Lecture on the neurone theory. Sherrington prepared some excellent photographs of Cajal's silver stained preparations, but Cajal would not use them. He said he wanted the assembled scientists to look into the microscopes provided to satisfy themselves on the seemingly fantastic revelations of which Cajal was speaking.

Sherrington's influence on neurophysiology and clinical neurology has been determinative. Philosophy and psychology have been changed by his scientific generalizations. Even the language of our science derived from his pen — a pen at home in verse, biography, and statesmanship as well. "Yet he was," as Sir Russell Brain has written, "the most modest of men, who felt, like Newton, that he had done no more than pick up a few pebbles on the shores of the great ocean of truth."[3]

Osler used to say that he took pride in having brought Sherrington to Oxford in 1913 as Waynflete Professor of Physiology. Little did Osler know what a bibliophile he had imported! In 1914 Sir Charles loaned his first edition of Descartes' *De homine* (1662) to Osler. Requiring it for a quotation (two years later!), Sherrington called at Osler's house in Norham Gardens for it. He was amused to read in Osler's hand the inscription on the first page: "Given to me, August 16, 1914 by C. S. Sherrington." Sir Charles immediately wrote below it: "Ex libris Gulielmi Osler 1914"

and replaced it on the shelf. When Sherrington, W. W. Francis and John Fulton were going over Osler's books prior to shipping them to McGill University in 1926 this Descartes item was found. This was not the first of Sherrington's treasures to come to Canada. In 1915 he presented to the library of the recently founded University of British Columbia his copy of Bidloo's Anatomy (1685), which had belonged at one time to Nicholas Hawksmoor, the architectural clerk of Christopher Wren. Sherrington had it inscribed by his friends who passed through his laboratory in that year, including Osler, John McCrae, Gowland Hopkins, Walter Raleigh, and Robert Bridges. This great tome was followed in 1938 by Laurentius Valla's *Elegance in Latin*, published in 1476 in Venice. This was inscribed by him, as he sat in his little rotating sunhouse at Ipswich in 1938, as a memorial to his early associate at Cambridge, Frank Fairchild Wesbrook, who later became the first President of the University of British Columbia.

Thus we come to the end of this all too-hasty survey of the student years of a group later distinguished in the neurological sciences. At a time when John Fulton's twenty-fifth anniversary as a professor at Yale is being celebrated it may be worth remembering that Fulton himself was a student contributor, essayist, and bibliophile. In the years 1930-1955 he opened his laboratory, his library, and often his purse to students who wanted to pioneer with their own investigations, however insignificant some might feel them to be. The tradition so long established in neurology must not be allowed to die.

REFERENCES

1. Babkin, B.: *Pavlov: A biography*. Chicago, University of Chicago Press, 1949. 365 pp.
2. Berlin, R.: *Beitrag zur Strukturlehre der Grosshirnwindungen*. Dissertation. Erlangen, A. F. Junge, 1858. 27 pp., 2 pl.
3. Brain, W. R.: *Presidential address, Royal College of Physicians*, 7 April 1952. London, Harrison and Son, 1952, p. 21.
4. Bravais, L. F.: *Recherches sur les symptomes et le traitement de l'epilepsie hemiplegique*. Thesis. Faculty of Medicine, Paris, 1827.
5. Dax, Marc: *Lesions de la moitie gauche de l'encephale coincidant avec l'oubli des signes de la parole*. Thesis. Montpellier, 1836.
6. Fulton, J. F.: *Selected readings in the history of physiology*. Springfield, Ill., Charles C. Thomas, 1930, p. xii.
7. Gennari, F.: *De peculiari structura cerebri nonnullisque eius morbis. Famose alnae anatom. observat. occidunt*. Parma, Regio Typographeo (Bodoni), 1782. xxvi, 87 pp., 4 pl.
8. Head, Henry: Ueber die negativen und positiven Schwankungen des Nervenstromes. Pflügers Arch. ges. Physiol., 1886-87, *40*, 207.
9. Head, Henry: On the regulation of respiration. J. Physiol. (Lond.), 1889, *10*, 1-70, 279-290.

10. Marie, P.: *Formes frustes of Basedow's (Graves') disease.* Thesis. Faculty of Medicine, Paris, 1883.

11. Russel, C. K.: Constantin von Monakow, 1853-1930. Arch. Neurol. Psychiat. (Chicago), 1935, *33*, 1088-1097.

12. Waller, A. V.: The microscopic observations on the perforation of the capillaries by the corpuscles of the blood, and on the origin of mucus and pus. Philos. Mag., 1846, *29*, 271-287; 397-405.

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DIENCEPHALIC MECHANISM OF CONTROL OF THE URINARY BLADDER OF THE CAT‡

It has long been known that at the level of the midbrain pontine junction there is a neural mechanism essential for micturition. Contraction of the urinary bladder in response to increased intravesicular pressure is abolished in the cat following a subcollicular, but not after an intercollicular decerebration.[1] Electrical stimulation of the brain stem at the level of the inferior colliculus evokes bladder contraction whereas bilateral chronic lesions in this area results in making cats incapable of completely emptying the bladder.[2] These experiments led Barrington to the conclusion that this area constitutes a reflex micturition mechanism. The presence of Barrington's micturition center in the brain stem has since been confirmed.[3, 4] In recent years, however, many investigators have stimulated more rostral portions of the brain and observed contractions of the bladder. These reactive regions are the rostral portion of the midbrain, and the posterior and anterior hypothalamus,[5] septum pellucidum and medial preoptic area,[6] the putamen and pallidum and the area around them as well as the genual gyrus,[7] and the cruciate sulcus.[8] Each of these areas described is in proximity to another reactive area, and therefore it is difficult to determine whether responses obtained by stimulation of the hypothalamus are due to excitation of cells or of fibers constituting a descending pathway. It is the purpose of this investigation to clarify this point by comparing (1) the bladder responses obtained following electrical stimulation of the hypothalamus in cats having chronic lesions at the preoptic level with (11) the responses obtained in normal animals.

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METHODS

In a series of 32 normal adult cats under chloralose (70 mg./kg. body weight, i.p.) or pentobarbital sodium (30 mg./kg., i.p.) anesthesia, the diencephalon and midbrain were electrically explored point by point through stereotaxically oriented concentric electrodes for bladder responses. The current was supplied by a Grass model S4 stimulator, which gives rectangular pulses. Stimuli of 2 to 6 volts, 2 to 60 per sec., and 10 msec. in pulse duration were routinely used. The bladder was exposed through a midline abdominal incision, and a plastic cannula inserted into the urethra and passed up into the bladder. In most experiments changes in bladder pressure were recorded by means of a water manometer, and in a few experiments by means of a tambour. An attempt was made to keep the initial pressure within the bladder at 60 to 80 mm. of water at the beginning of each experiment. Blood pressure was recorded from the femoral artery with a mercury manometer, and respiration by means of a pneumograph and tambour arrangement.

In 11 cats, electrolytic or radioactive lesions were placed in the preoptic region with the aid of a stereotaxic instrument.* Pentobarbital was used for anesthesia. The electrolytic lesions were made in 4 cats (63, 64, 67, and 68) by passing a direct current of 3.0 ma. for 60 sec. through insulated bipolar electrodes with the tips exposed for a length of about one centimeter.

Lesions with implanted radioactive substances were made in the other 7 cats. In cat 54, three glass radon seeds (0.4 mm. in diameter, 6.0 mm. in length, and each containing 0.02 millicurie) were implanted in a row across the preoptic area. Radon emits both beta and gamma rays and has a half life of 3.85 days. In three cats (56, 57, and 58), three rods of radioactive palladium[107] were deposited in the preoptic area of each cat with a specially built attachment for the stereotaxic instrument.† Three palladium rods (0.8 mm. in diameter and 8 mm. in length) were first encased in a polysterene block through which three parallel holes had been drilled for them. The block was then subjected to neutron bombardment at the Brookhaven reactor. At the time of operation the polysterene block was mounted on the attachment, and the radioactive palladium rods were deposited in the preoptic region. Each was estimated to have 2.0 millicuries of beta radioactivity with a half life of 13 hours. Palladium spheres were used in cats 41, 45, and 48. Two palladium spheres (1.0 mm. in diameter, with 2.0 millicurie radioactivity each) were placed in the preoptic region with a modified stereotaxic manipulator‡ (for technique, see Boyesen and Campbell[4]). Lesions produced by radioactive substances were slowly progressive and were usually not maximal until 5 to 14 days had elapsed. The common characteristic of the lesions in all 11 cats was that they separated the hypothalamus from the telencephalon at the level of the anterior commissure. After periods ranging from three weeks to two months, the cats were anesthetized with chloralose and the normally reactive areas in the hypothalamus and mid-

* Ledercillin Parenteral was used during the postoperative recovery period, and the antibiotic was supplied to us in generous amounts by Lederle Laboratories Division.

† We wish to express our gratitude to Dr. Harald H. Rossi of the Department of Radiology, Columbia University, for his helpful suggestions in designing the instrument, and to the Engineering Department of Becton, Dickinson & Co., Rutherford, N. J., for constructing the first pilot model.

‡ We wish to express our appreciation to Dr. Svein Boyesen for preparing these cats with lesions produced by the radioactive palladium spheres.

brain were excited using the same technique as in the control experiments. At the end of each acute experiment, the brain was perfused with 10% neutral formalin, and subsequently embedded in celloidin and sectioned at a thickness of 25 μ. Selected sections were stained with a Nissl or Weil stain and examined in order to determine the extent of the lesion and the location of points from which contractions of the bladder were elicited.

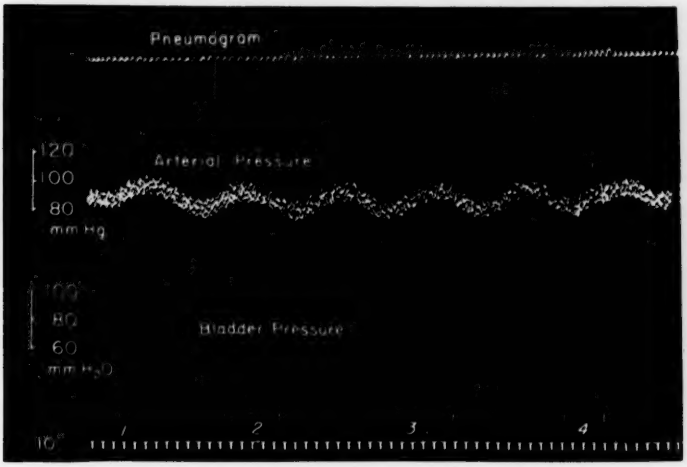

FIG. 1. Bladder responses following stimulation of the medial preoptic area with low frequencies. Cat 9, weight 2.8 kg. Pentobarbital anesthesia. Respiratory movements recorded with pneumograph and tambour, arterial pressure with mercury manometer connected to the femoral artery and bladder pressure recorded with water manometer. Time marker, 10-second intervals.

At 1. Stimulated with 5.2 volts and 8 per second.

At 2 and 3. Frequency reduced to 4 and 2 per second, respectively. The response at 3 resembles the spontaneous contractions of the bladder.

At 4. Repeated at 8 per second, a large contraction of the bladder was again obtained.

RESULTS

Bladder responses in normal cats. It appeared that under chloralose anesthesia the urinary bladder exhibited spontaneous changes in tone more often than under pentobarbital anesthesia and was generally more reactive upon central stimulation. The responses thus elicited usually had a latency of two to three seconds, while in another two or three seconds a maximum pressure of about 60 to 120 mm. of water was reached; this was usually sustained for the duration of stimulation. In stimulating the septal and preoptic area with a weak current, the bladder response was a series of small contractions resembling the normal spontaneous activity of the bladder, or

a larger contraction consisting of several step-like contractions. If the strength of the current was increased from 2 or 3 to 5 volts, or the frequency of the stimulus was increased from 2 to 10 or 15 per second, the series of bladder contractions previously obtained with the weak stimulus was fused into a smooth contraction (Fig. 1). With higher frequencies

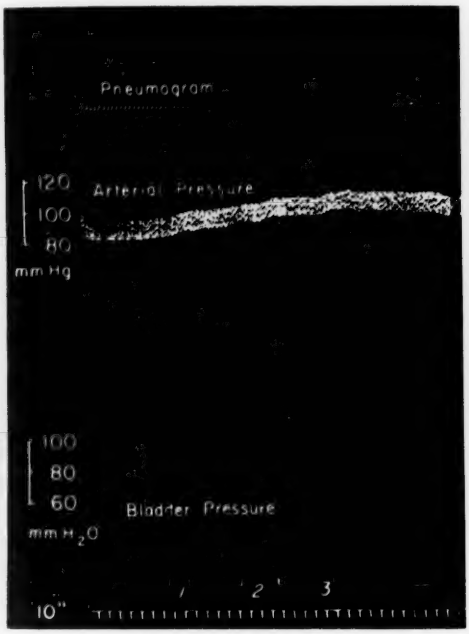

FIG. 2. Bladder responses following stimulation of the ventromedial hypothalamus with various frequencies. Cat 10, weight 3.0 kg. Pentobarbital anesthesia. Other details as in Figure 1.

At 1. Stimulated with 6 volts and 10 per second.
At 2. Stimulated at 5 per second.
At 3. Stimulated at 30 per second.

such as 20 to 60 per second, the bladder responses were usually as large, or larger (Fig. 2). Only occasionally did stimulation at the higher frequencies produce a fall of bladder pressure. This occurred especially when the bladder exhibited relatively high initial pressure and vigorous spontaneous contraction. When the hypothalamus was stimulated at low frequencies, such as 10 per second, unsustained responses were also occasionally observed.

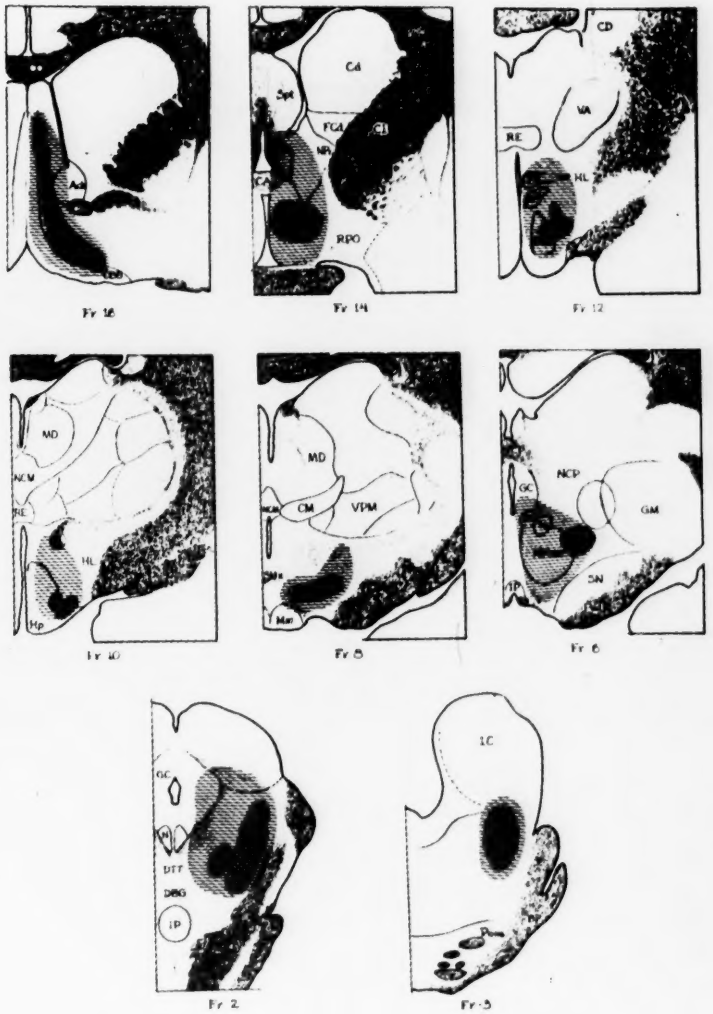

FIG. 3. Composite drawings of a few selected coronal sections of the cat's brain indicating responsive regions for sustained bladder contractions. Horizontal-lined, moderate responses; cross-hatched, marked responses. The number under each figure represents the distance in mm. from the inter-aural plane of the stereotaxic instrument. For details and abbreviations, refer to Jasper and Ajmone-Marsan[8]

Stimulation at the level of the caudal portion of the midbrain ventral to the inferior colliculus always produced maximal bladder contractions. These were associated with pressor responses, apnea, and arching of the back. A constant relationship between bladder contraction and vasomotor or respiratory responses was not found in any other area stimulated.

The distribution of the reactive points at different levels of the forebrain, diencephalon, and the midbrain is shown in a series of cross sections (Fig. 3), which are very similar to those reported by Kabat, *et al.*[7] and Wang and Ranson.[14] In the forebrain the anterior border of the reactive area was about 2 mm. rostral to the anterior commissure. The reactive regions correspond to the septum pellucidum, the area around the anterior commissure and stria terminalis, and the medial preoptic areas. At the level of the diencephalon, bladder responses could be obtained diffusely in the hypothalamus, particularly around the fornix and the supramammillary commissure. At the level of the midbrain, the reactive points were located in the lower and peripheral portions of the periventricular gray matter, and diffusely in the tegmentum about the central tegmental tract. At the most caudal region stimulated, a highly reactive area lay just ventral to the inferior colliculus and medial to the brachium conjunctivum.

Chronic lesions in the preoptic region. After recovery from the operations, the animals were in good health and ate well. Despite the large size of the lesions made (Fig. 4), especially with the radioactive palladium rods (Fig. 5), the cats were in excellent condition, possibly due to the fact that the lesions developed slowly over several days and might have allowed time for compensation within the nervous system. There was, however, one interesting neurological involvement shown by most of the operated cats. This consisted of the development of alternate rhythmic flexion of the forelimbs, which occurred while the animals were standing or lying, or when held with their feet suspended in the air. With each flexion of the forelimbs the claws were adducted and with each extension the claws were abducted. In some of the cats this rhythmic motion was associated with a posture, including arching of the back and flexion of the hind limbs while standing. These cats were very clumsy at running and usually held their tails and hind limbs extended. No other behavioral changes were observed.

Bladder responses in cats with chronic preoptic lesions. In these operated animals, it was relatively difficult to find points that yielded bladder contractions and, when found, the size of the contractions was always small, about one quarter of the normal pressure increase in most cases (Fig. 6). Characteristic of the responses obtained on stimulation of the hypothalamus

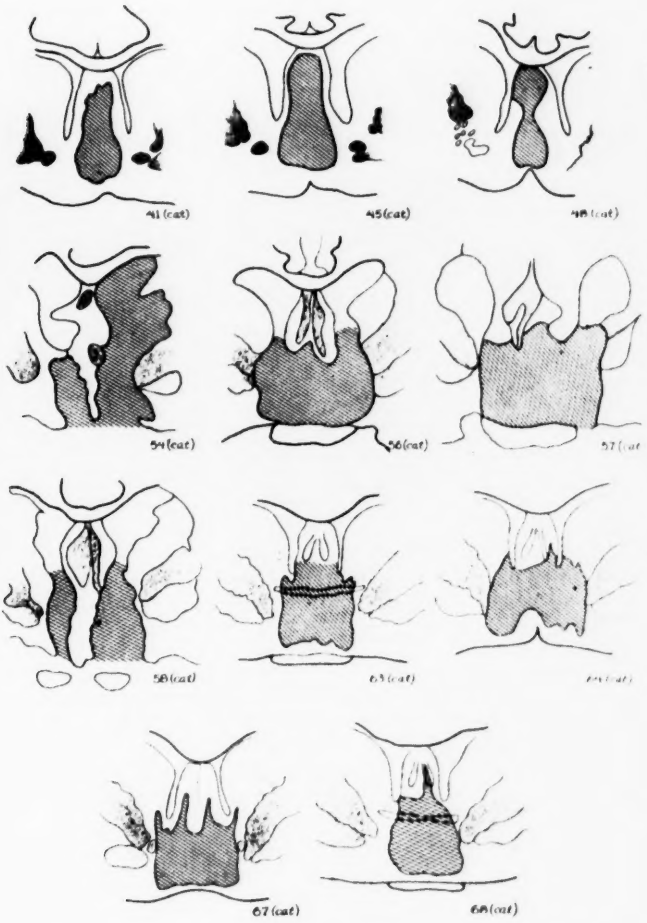

FIG. 4. Composite drawings of coronal sections through the lesions of the eleven cats with lesions in the preoptic area. The lined area indicates maximal destruction lesion. Cats 41, 45, and 48—lesions made by radioactive palladium spheres. Cat 54—lesions made by radon seeds. Cats 56, 57, and 58—lesions made by radioactive palladium rods. Cats 63, 64, 67, and 68—lesions made by electrolysis.

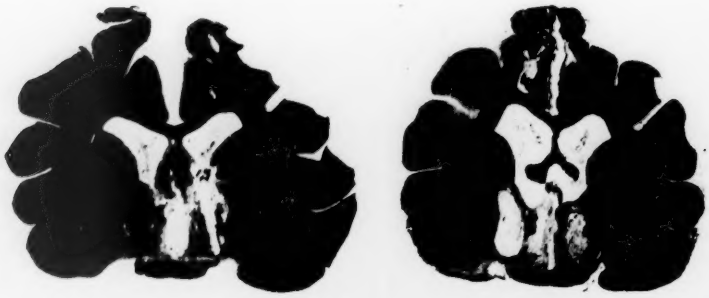

FIG. 5. Photomicrographs of the brain at the level of the optic chiasma showing lesions made by the radioactive palladium rods. Cats 56 and 57.

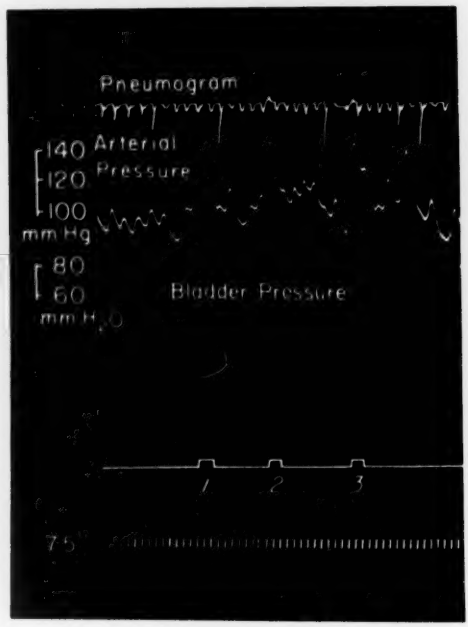

FIG. 6. Bladder responses following stimulation of the posterior hypothalamus in cat 57 with lesion shown in Figure 5. Weight 2.6 kg. Chloralose anesthesia. Time marker 7.5 second intervals. Other details as in Figure 1.

At 1, 2, and 3. Three different points stimulated with 5 volts and 10 per second. Note that the bladder contractions were small and are not sustained and were accompanied by pressor responses.

was that, in addition to being smaller, they rose to their maximum pressure in about seven seconds and then abruptly declined with the bladder relaxing to its resting volume in ten to fifteen seconds despite the continued stimulation (Fig. 6 and Fig. 7, points 3 and 4). The bladder responses, when obtained, were usually accompanied by pressor responses.

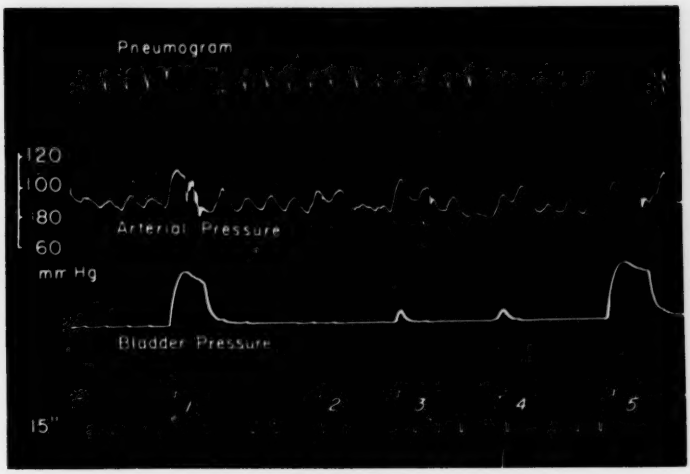

FIG. 7. Bladder responses following stimulation of the caudal midbrain and the posterior hypothalamus in cat 68 with lesions shown in Figure 4. Weight 3.1 kg. Chloralose anesthesia. Bladder pressure recorded with a rubber membrane tambour. Time marker 15 second intervals. Other details as in Figure 1.

At 1. A point at the caudal midbrain level (Barrington's micturition center) stimulated with 8 volts and 30 per second. Note the large sustained contraction, which was obtained on stimulating the same region later at 5.

At 2, 3, and 4. Three different points in the posterior hypothalamus stimulated with 8 volts and 10 per second. Note that only small unsustained contractions of the bladder were obtained.

In all the operated cats only once was a sustained bladder response obtained following stimulation of the hypothalamus (cat 48); in this animal the lesion was found to be relatively small (Fig. 4).

The most rostral level at which bladder responses were obtained in animals with preoptic lesions was a section through the anterior hypothalamic area (Fig. 8). Seven cats were stimulated at this level. Responses were obtained only in cat 54, in which the lesion did not completely obliterate the lower part of the septum pellucidum. The most rostral level at which responses were consistently obtained was at the level of the rostral border of the ventromedial hypothalamic nucleus. The reactive points were in that

nucleus and grouped medially and laterally in the region of the column of the fornix. At the level of the rostral border of the posterior hypothalamus one out of the three cats stimulated gave relatively large unsustained

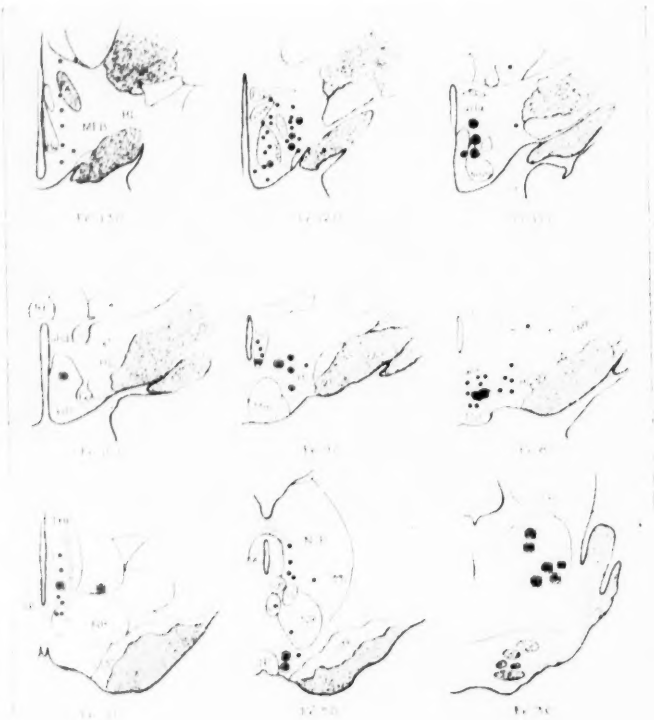

FIG. 8. Composite drawings of a few, selected coronal sections of the brain indicating responsive regions for bladder responses in cats with chronic preoptic lesions. *Dot*, unsustained contractions with pressure rise of 1-20 mm. H_2O; *dot within circle*, 21-40 mm. H_2O; *dot within two circles*, 41-60 mm. H_2O; *single or double circles within squares*, sustained bladder contractions.

responses, which were grouped medially to the column of the fornix, near the posterior hypothalamus nucleus and the caudal portion of the ventromedial hypothalamic nucleus. All six cats stimulated at the level of the rostral border of the mammillary bodies gave unsustained contractions of moderate size. The responsive points were in the posterior hypothalamic nucleus and in the lateral hypothalamic area. All four cats stimulated at a

level through the middle of the mammillary bodies gave small or moderate responses throughout the supramammillary commissure and lateral hypothalamic area. At the level of the posterior commissure small responses were obtained about the central gray in four of the seven cats stimulated. At the level of the inferior colliculus large, sustained responses were obtained in all of the five cats stimulated (Fig. 7, points 1 and 5).

In one cat in which radioactive palladium spheres were placed too anteriorly, normal sustained bladder contractions were evoked on stimulation of the hypothalamus.

DISCUSSION

Typical bladder responses obtained from preoptic or diencephalic points are either a series of small contractions or a smooth, sustained contraction for the duration of electrical excitation, depending upon the strength or frequency of the stimulus (Figs. 1 and 2). These responses have been shown to be mediated by the parasympathetic nerve supply to the bladder through the sacral roots.[11] As is well known, it is not possible to determine whether the cells or the fibers in the responsive area are being stimulated. However, since the general opinion in regard to the conduction of visceral impulses in the brain stem favors conduction by chains of short neurons, as Kabat, *et al.*,[7] suggested, it is possible that both cells and the fibers in the reactive region take part in the forwarding of impulses to the bladder and that there may be many synapses between the preoptic area and the level of the inferior colliculus. The absence of the sustained "parasympathetic" type of bladder responses in cats with chronic preoptic lesions as shown in the present series of experiments indicates that very few, indeed if any, of the cells representing the bladder in the preoptic area could synapse before reaching the micturition mechanism at the midbrain pontine junction.

The small, unsustained responses elicited from the medial and posterior hypothalamus in the cats with chronic preoptic lesions resemble those occasionally elicited from the same areas in the control preparations. It may be argued that these small contractions obtained in cats with chronic lesions resulted from stimulation of a few relay neurons in the hypothalamus or from stimulation of small numbers of fibers descending from cells not obliterated by the lesion. However, this type of unsustained response is not generally associated with submaximal stimulation; when it is, a series of small contractions generally results (Figs. 1 and 2). On the other hand, unsustained contraction of the bladder has been reported to occur upon

stimulation of the hypothalamus after section of the sacral roots or atropinization.[18] The responses also resemble the unsustained contractions of the bladder which result from stimulation of the peripheral sympathetic nerve supply to the bladder.[10, 18] The association of these responses with pressor reactions suggests that they may be mediated through the sympathetic supply to the bladder. It is to be pointed out here that according to Beattie and Kerr[2] stimulation of the posterior hypothalamus yielded a fall in the intravesicular pressure, which they interpreted as due to excitation of the sympathetic supply to the bladder. This discrepancy in the bladder responses obtained from the hypothalamus might be related to the initial tonus of the bladder and also to the frequency of the stimulus used.

The function of the medial and posterior hypothalamic bladder representation in the act of micturition is not clear. The small, unsustained contractions obtained there on stimulation may represent contraction of the trigone. Fibers from the preoptic region may synapse with the cells in the posterior hypothalamus for the purpose of integrating the influences on the bladder acting through both parasympathetic and sympathetic innervation.

The depth of anesthesia maintained in acute stimulation experiments may influence the extent to which a pattern of activity can be evoked from a point. However, the responsive region at the level of the caudal midbrain is the only one stimulated which gives any indication of being a center for micturition in the sense that it appears to be capable of coordinating autonomic and somatic responses into a fragmentary representation of the act of micturition.

CONCLUSIONS

Sustained bladder contractions were elicited in cats by stimulation of the preoptic area, the septum pellucidum, the medial and lateral hypothalamus, the central gray matter, and the area about the central tegmental fasciculus in the midbrain. In animals with preoptic lesions, stimulation of the hypothalamus did not yield such sustained bladder responses, suggesting that in the intact animals the sustained bladder responses were due to stimulation of fibers with their cells of origin located in the septum pellucidum and medial preoptic area. In these animals, small, abrupt and unsustained contractions of the bladder were occasionally obtained on stimulating the ventromedial and posterior hypothalamus and rostral midbrain. These results are discussed in terms of the sympathetic and parasympathetic innervation of the bladder.

REFERENCES

1. Barrington, F. J. F.: The relation of the hind brain to micturition. Brain, 1921, *44*, 23.
2. Barrington, F. J. F.: The effect of lesions of the hind- and mid-brain on micturition in the cat. Quart. J. exp. Physiol., 1925, *15*, 81.
3. Beattie, J. and Kerr, A. S.: The effects of diencephalic stimulation on urinary bladder tonus. Brain, 1936, *59*, 302.
4. Boyesen, S. and Campbell, J. B.: Stereotaxic implantation of artificially produced radioactive isotopes: a technic for producing quantitated lesions in the brains of laboratory animals. J. comp. Neurol. (In press)
5. Hess, W. R. and Brugger, M.: Der Miktions- und der Defakationsakt als Erfolg zentraler Reizung. Helv. physiol. pharmacol. Acta, 1943, *1*, 511.
6. Jasper, H. H. and Ajmone-Marsan, C.: *A stereotaxic atlas of the diencephalon of the cat.* The National Research Council of Canada, Ottawa, Canada.
7. Kabat, H., Magoun, H. W., and Ranson, S. W.: Reactions of the bladder to stimulation of points in the forebrain and midbrain. J. comp. Neurol., 1936, *63*, 211.
8. Langworthy, O. R. and Kolb, L. C.: The encephalic control of tone in the musculature of the urinary bladder. Brain, 1933, *56*, 371.
9. Langworthy, O. R. and Kolb, L. C.: Demonstration of encephalic control of micturition by electrical stimulation. Bull. Johns Hopkins Hosp., 1935, *56*, 37.
10. Langworthy, O. R., Reeves, D. L., and Tauber, E. S.: Autonomic control of the urinary bladder. Brain, 1934, *57*, 266.
11. Strom, G. and Uvnas, B.: Motor responses of the gastro-intestinal tract and bladder to topical stimulation of frontal lobe, basal ganglia and hypothalamus in the cat. Acta physiol. scand., 1950, *21*, 90.
12. Tang, P. C. and Ruch, T. C.: Non-neurogenic basis of bladder tonus. Amer. J. Physiol., 1955, *181*, 249.
13. Wang, S. C. and Harrison, F.: The nature of bladder responses following stimulation of the anterior hypothalamus. Amer. J. Physiol., 1939, *125*, 301.
14. Wang, S. C. and Ranson, S. C.: Descending pathways from the hypothalamus to the medulla and spinal cord: observations on blood pressure and bladder responses. J. comp. Neurol., 1939, *71*, 457.

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ELECTRICAL ACTIVITY OF THE CEREBELLUM IN THE INTACT AND DECEREBRATED CAT: THE RÔLE OF THE PONTINE STRUCTURES

The characteristics of the cerebellar electrical activity as first described by Adrian in 1935 and confirmed by Dow in 1938 consist of groups of diphasic waves at frequencies ranging from 150-250 per sec., the amplitude being about 10 microvolts. Further confirmation was given in 1951 by Brookhart, *et al.*,[3] who recorded from the anterior lobe of cerebellum of unanesthetized cats, subjected to intercollicular decerebration. These authors distinguished two kinds of activity, waves and spikes, both originating from structures in the Purkinje cell and granule cell layers, distinguished by their different susceptibility to ischemia. Occasional waves at a frequency of 10 per sec. appeared to be due to extracerebellar sources.[18]

Lately, however, different views have been advanced. The activity of the cerebellum recorded from unanesthetized cats after intercollicular decerebration seems to consist of waves of much bigger amplitude, i.e. from 50-80 microvolts[10] to 100 microvolts or more.[13] Low frequencies have also been observed in decerebrated cats, i.e. 50 per sec.[14]

The higher amplitude and lower frequency activity has been attributed to better conditions in the preparation; the authors claim that using a vacuum pump as they do for the section (destruction) of the brain stem, the basal arteries are less injured than by section with a knife and no compression of the vertebral arteries is needed; blood flow in the common carotids needs to be stopped only for a brief time. This technique has also been used by Bremer and Bonnet.[2]

We thought that the best physiological condition of the cerebellum ought to be established carefully because investigations on the activity of this organ may lead to different results if the preparation is different. Nulsen, *et al.*,[15] found that cortically induced movements and knee jerks in lightly anesthetized monkeys (with intact nervous system) were facilitated by high frequency stimulation (80-100 per sec.) of the anterior lobe of the cerebellum, while low frequency (10-40 per sec.) of the same focus gave inhibition. Moruzzi,[11, 12] on the other hand, found that high frequencies in-

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hibited and low frequencies facilitated myotactic reflexes and decerebrate rigidity. These authors investigated two different phenomena, but this does not justify in our opinion an opposite action on the same cerebellar centers due to stimulation of the same frequency.

Martini, *et al.*,[1] and Gualtierotti, *et al.*,[2] reported that in cats subjected to intercollicular decerebration a high intensity electrical stimulation of the vermis of the cerebellum produced electrical silence that outlasted the end of the stimulation and that could not be produced again when the same stimulation was repeated after a retrocollicular section; decerebration was performed with the usual Sherrington technique, spontaneous electrical activity of the cerebellum being no more than 20-30 microvolts. These results have been confirmed by Moruzzi,[3] but only when the activity of the cerebellum was of the said amplitude; when the activity of the cerebellum was 80-120 microvolts, as by the new technique used, no such finding was obtained.

The purpose of this paper is the investigation of the changes at the various stages of decerebration using different techniques (starting from the intact animal), and their bearing on the different electrical behaviors reported.

METHOD

A couple of silver chloride (wire diameter 0.8 mm.) electrodes, insulated except for the tip, were screwed 4 mm. apart to the skull of cats under light N.O and ether anesthesia. Position of the electrodes was such as to reach the lobus anterior of the cerebellum so that the naked tips of the electrodes were completely submerged in the cortex. The electrodes were very steadily fixed, and the normal movements of the animal gave only negligible mechanical artifacts. Records were taken as follows:

(i) After complete recovery from anesthesia, the animal was free to move within the limitation imposed by the length of the recording wires.

(ii) The animal was then lightly anesthetized again, the common carotids were exposed and tied.

(iii) The skull was then opened and decerebration performed with a single intercollicular cut, compression of the vertebral arteries being maintained for a short time (*ca.* 2-3 min.).

(iv) Alternately to (iii), the common carotids were only compressed for a short time, while decerebration was performed by means of a suction of the anterior colliculi till the brain stem was interrupted; the cerebral masses in front of the cut were removed by suction.

No appreciable hemorrhage was observed in the case of either (iii) or (iv), and artificial respiration was not needed in most of the cats. Anesthesia was discontinued after decerebration.

Electrocerebellograms were recorded at each stage of the experimental routine, either with continuous record or using the time base running with a duration of 50 msec.

RESULTS

INTACT ANIMAL

The activity of the cerebellum in the intact unanesthetized cat, as described in (1), consisted of three different kinds of waves (Fig. 1a and 2a):

(a) Fast diphasic waves of a frequency ranging between 150 and 300 per sec., maximum amplitude being 25 microvolts, average 15 microvolts.

(b) Spikes, their frequency reaching up to 1000 per sec.; amplitude less than 10 microvolts.

(c) Slow waves: frequency 10 to 40 per sec. of up to 50 microvolts. Over all maximum amplitude due to summation of factors (a) and (b) was 40 microvolts.

EFFECT OF ANESTHESIA

During light anesthesia, when all voluntary movements were abolished but reflexes were brisk and muscular tonus seemingly unimpaired, the only alteration observed was the nearly complete disappearance of the slow waves as in (c) (Fig. 2b). Both kinds (a) and (b) of fast activity were completely unchanged in frequency and amplitude. A much deeper anesthesia was required before a decrease in amplitude could be observed.

OCCLUSION OF COMMON CAROTIDS

No further change was observed immediately after the common carotids had been tied and within one hour's time (Fig. 1b).

SURGICAL SECTIONS OF THE BRAIN STEM

The opening of the skull and all operations needed to expose the colliculi did not alter appreciably the activity described above; only a slight increase in amplitude was observed in some cases.

The intercollicular section performed during compression of the vertebral arteries did not change in a significant way the cerebellar activity; Figure 1c records were taken after release of the vertebral arteries.

A postcollicular section made without any additional anesthesia, with a second transitory compression of the vertebral arteries changed the electrical activity as follows (Fig. 1d):

(a) The fast waves, though maintaining the same frequency, increased slightly in amplitude, up to 30-35 microvolts.

(b) Spikes appeared unchanged in frequency and amplitude.

(c) Slow waves of a new character were recorded, their frequency being about 50 per sec. and their amplitude reaching up to 80 microvolts.

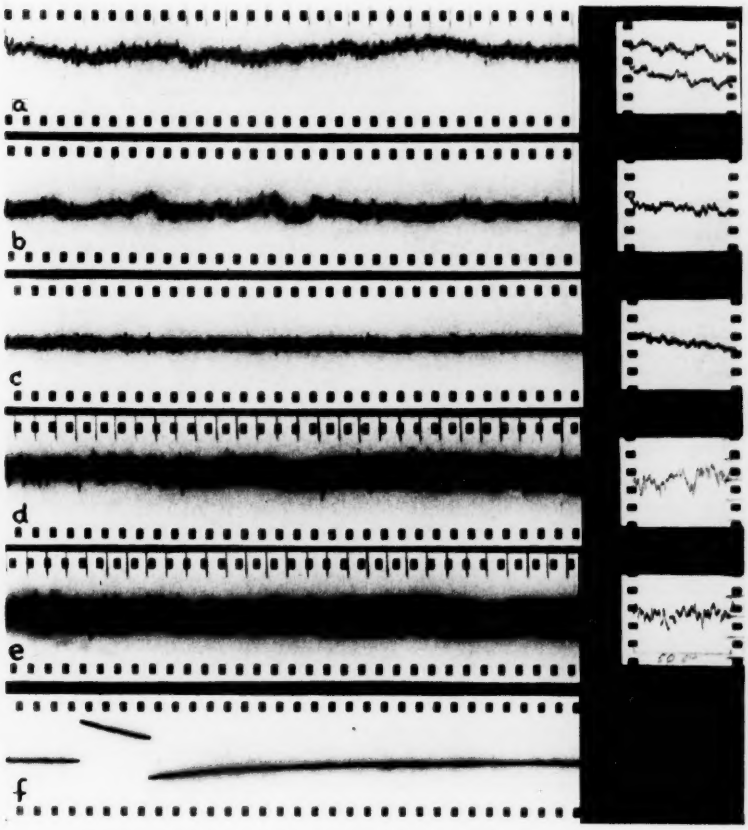

FIG. 1. Electrical activity of the cerebellar cortex of cat (lobus anterior): continuous record on the left; activity recorded during 50 msec on the right.

(a) Unanesthetized intact animal;

(b) After occlusion of the carotids and light N_2O and ether anesthesia; no appreciable change is detectable;

(c) After intercollicular surgical decerebration; slow waves disappear;

(d) After retrocollicular decerebration; over all amplitude is increased and a slow rhythm appears;

(e) An hour after retrocollicular decerebration; the activity is slightly decreased and the slow rhythm increases in frequency.

Time marker: 1/20 sec.

Record on the bottom: 100 microvolts deflection.

The over-all activity seen in normal tracings appeared to exceed 100 microvolts owing to the fact that fast activity of both kinds was inscribed on top of the slow waves and graphical summation of amplitude took place. This was quite evident in the 50 msec. time base recording.

In about 1-2 hours this larger amplitude activity slightly decreased, over-all values going down to 60-80 microvolts. The frequency of the slowest waves increased up to 70 per sec. (Fig. 1e).

DECEREBRATION BY SUCTION

When transcollicular decerebration was performed by suction, records taken during the operation showed a remarkable increase of the slow activity (waves of 10-40 per sec., Fig. 2c). It must be remembered that this activity had been greatly reduced because of the anesthesia. Sometimes bursts of very large spikes, even exceeding 200 microvolts (Fig. 2d), were recorded during the first attempt at suction on the brain stem.

In most experiments interruption of the brain stem was made as quickly as possible to avoid hemorrhage. After decerebration the cerebellar activity showed the same changes as after the postcollicular surgical section in the Sherrington preparation (Fig. 2e); the apparent increase in amplitude due to the new large and slower waves took place at this stage. In these conditions a further surgical postcollicular section, also if performed under anesthesia, did not produce any change in electrical activity (Fig. 2f).

If a deep anesthesia was applied or if the blood pressure was lowered, reduction in the amplitude and frequency of the cerebellar activity was observed. It seemed that the new large waves were particularly susceptible to variations in anesthesia and blood pressure.

When a surgical section between the two colliculi with tied common carotids, but without any compression on the vertebral arteries, was followed by quick removal by suction of the encephalon cranial to the cut, hemorrhage being stopped by application of hemostatic sponge, results were as obtained by the simple Sherrington technique of decerebration. Variations in cerebellar activity as described above were obtained only after postcollicular section. This experiment was devised to test the possible influence of mechanical traction on the fibers of the brain stem as an effect of suction, which does not occur after a previous section of the brain stem.

DISCUSSION

All the results obtained so far seem to prove that in the intact unanesthetized cat the electrical cerebellar activity proper is composed as described by the earlier investigators of:

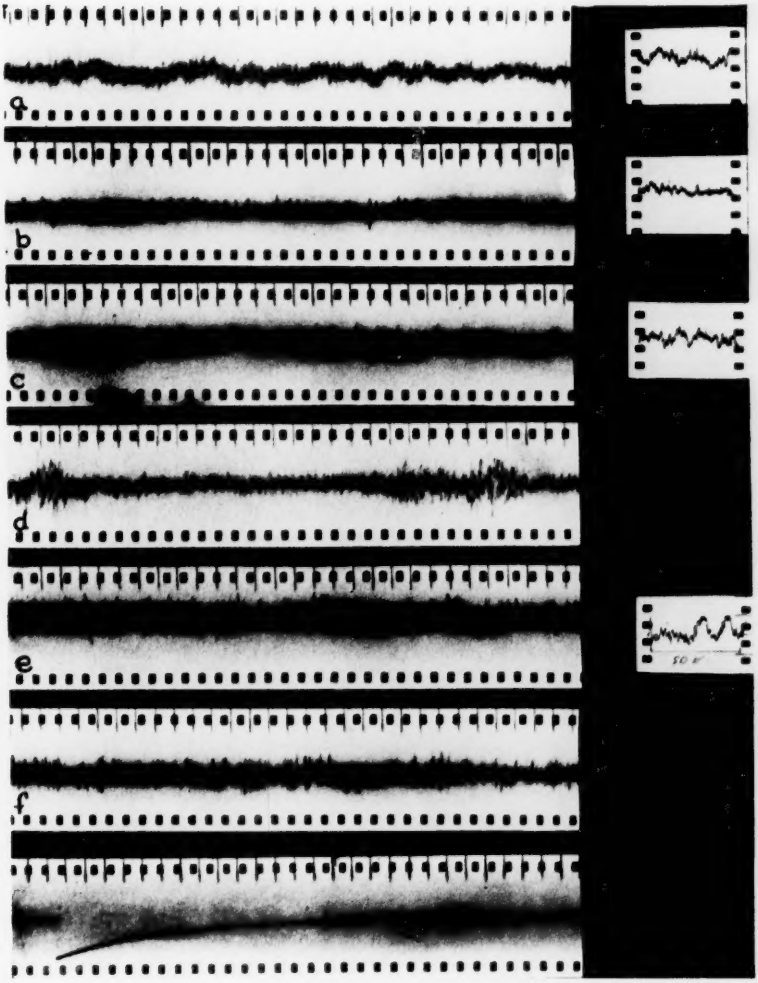

FIG. 2. Electrical activity of the cerebellar cortex of the cat, recorded as in Figure 1.
(a) Unanesthetized intact animal;
(b) After light N_2O and ether anesthesia;
(c) and (d) Incomplete decerebration by suction; slow activity reappears and bursts of fast large amplitude activity are evident;
(e) Decerebration by suction is ended: 1/4 hour after compression of the carotids, initiated between (b) and (c), was removed, the tracing has the same aspect as Figure 1d;
(f) After retrocollicular surgical section; no appreciable change from the preceding.
Time marker: 1/20 sec.
Record on the bottom: 100 microvolts deflection.

(a) Biphasic waves at a frequency of 150-300 per sec. and with an average amplitude of 15-20 microvolts;

(b) Spikes at a frequency of up to 1000 per sec. and with an amplitude averaging 10 microvolts.

The slow waves, as was already pointed out by Ten Cate and Wiggers,[18] are presumably spread from the cerebral cortex: in fact, both a light anesthesia and the tying of the common carotids decrease remarkably this rhythm, as on cerebral cortex itself.

The cerebellar potentials from a record taken at a slow speed show an apparent amplitude reaching at some points 40-50 microvolts. This is presumably to be interpreted as the summation by chance of waves and spikes. Similar values of the electrical activity of cerebellum were given in pigeons decerebrated rostrally to the optic lobes by Crepax and Pompeiano[7] and in the intact pigeon by Gualtierotti and Schreiber (in preparation).

Neither a light N_2O and ether anesthesia, nor the occlusion of the carotids alters the cerebellar potentials. This result was expected, in view of the fact that the carotids carry but little of the blood supply to the cerebellum, and a light N_2O and ether anesthesia is presumably only effective on the cerebral cortex, which shows a lower threshold to these drugs.

A fundamental difference exists between decerebration by surgical section according to the Sherrington technique and decerebration by suction, the only advantage of the latter being that the vertebral arteries need not be compressed during the operation; the occlusion of the carotids has in fact no influence on the cerebellar activity proper.

Decerebration by suction seems to alter remarkably the electrical activity of the cerebellum compared with the one recorded from an animal as much as possible intact; the most characteristic change due to decerebration by suction is the appearance of slower and larger potentials which remain practically unchanged for several hours. After decerebration by surgical section the potentials remain the same as in the animal in the best physiological condition.

A short compression on the vertebral arteries does not seem to alter appreciably the spontaneous activity of cerebellum.

A similar change of cerebellar potentials as due to decerebration by suction is observed after a postcollicular surgical section performed according to the Sherrington technique.

Since removal by suction in itself does not produce any change in the electrical activity of the cerebellum if a transcollicular section is previously performed, it is presumed that the increase of the electrical potentials and the appearance of a slow rhythm induced by decerebration by suction are due to a mechanical action on the fibers, an action which affects areas ex-

tended much further than the site of suction and which induces a modification of the activity of the pontine nuclei.

The slow rhythm, high potential cerebellar activity found in these conditions is not a technical artifact, but a biological effect, as it has been demonstrated by applying novocaine to the cortex.[3]

Pontine centers have the capacity for inducing a slow electrical activity on the cerebellar cortex as has been shown by Gualtierotti and Capraro[5] and later by Bremer and Bonnet,[2] either by applying strychnine on the floor of the fourth ventricle or by electrical stimulation. Similar results were also

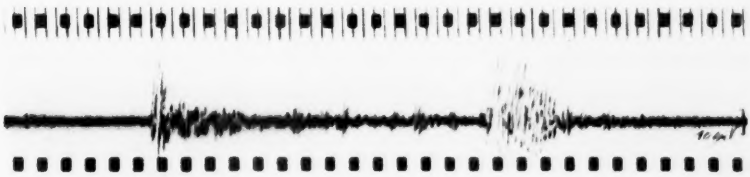

FIG. 3. Record of cerebellar activity in the intact pigeon taken with electrodes covering about 40 Purkinje cells during vestibular stimulation as given to the animal for a 315° turn of the contention table. The first burst is coincident with the start, the onset of the second burst marks the stop: start and stop are tangential acceleration stimuli. Between the bursts the labyrinth was subjected to centripetal acceleration only.

The vastly increased activity induced by tangential acceleration is composed of large waves at a much lower frequency than the potentials recorded from the unexcited cerebellar cortex.

Time marker: 1/20 sec.

reported by Mollica and Naquet.[7] The frequency and amplitude of the slow activity induced on the cerebellum was roughly proportional to the stimulation applied to the pontine centers.

It might be supposed that suction of the brain tissue, even if applied perpendicularly to the brain stem or directed towards its cranial end, is bound to produce a severe traction on the bulbopontine tracts if it has such a power to destroy the continuity of the brain stem itself. This traction causing tearing of the fibers appears in our opinion an extremely injuring procedure; the injury may possibly extend to the caudal part of the brain stem as far as the medulla. From the injured fibers a continuous flow of stimuli may well reach the pontine structures, inducing the slow waves recorded from the cerebellar cortex, as during strychnine application or electrical stimulation. Moreover, the lack of effect of a postcollicular section could be due to the abnormal conditions of the bulbopontine nuclei.

The nature of slow waves recorded from the cerebellar cortex of the transcollicular cat needs further investigation. Bremer and Bonnet[2] con-

sider the slow cerebellar waves that follow strychnine application or electrical stimulation as electrical seizures; the cerebellar cortex of animals decerebrated by suction could then be considered as being a subepileptic condition. This would explain why the threshold for electrical stimulation in these conditions is so low.[17, 18]

On the other hand, Gualtierotti and Schreiber (in preparation) have shown that volleys of impulses from the labyrinth induce on the vermis large synchronized potentials at a low frequency (60-80 per sec.) and with an amplitude of up to 200-300 microvolts (Fig. 3). This shows that slow waves are not necessarily due to a convulsive activity of the cerebellum, but also to afferent sensory volleys reaching the cerebellar cortex from any other part of the central nervous system, i.e., a conducted activity not necessarily convulsive.

The spikes of increased amplitude and number recorded in these conditions could represent the efferent discharges produced as a response to sensory stimulation by the cerebellar neurones.

SUMMARY

1. Three kinds of waves may be evidenced as the cerebellar electrical activity in the unanesthetized intact cat: (a) fast diphasic waves, 150-300 per sec., 15-25 microvolts in amplitude, and (b) spikes, up to 1,000 per sec., less than 10 microvolts in amplitude, are cerebellar activity proper; the third, (c), slow waves, 10-40 per sec., up to 50 microvolts in amplitude, are presumably transmitted from the cerebrum.

2. A light N_2O and ether anesthesia induces no changes in activity (a) and (b), but abolishes or decreases remarkably the waves (c).

3. Permanent occlusion of the common carotids and short compression of the vertebral arteries do not interfere noticeably with cerebellar electrical activity.

4. Intercollicular surgical decerebration does not impair significantly the cerebellar activity in comparison with that recorded from intact cats under light anesthesia.

5. Postcollicular decerebration increases up to 10-15% fast waves (a), no change being recorded in spikes (b), and induces new slow waves (d) at the frequency of about 50 per sec. and with an amplitude of 80 microvolts.

6. One to two hours after postcollicular decerebration a slight decrease in waves (d) was observed; their lowered amplitude averaged 60 microvolts.

7. Intercollicular decerebration made by suction in anesthetized cats (N_2O and ether) induces during the operation new volleys of 10-40 per

second slow waves (c), and bursts of fast waves at a frequency of 150–300 per sec. and with an amplitude of 150 microvolts.

8. After complete intercollicular decerebration by suction, the cerebellar electrical activity becomes very similar to that recorded after postcollicular surgical section: a slight increase in fast waves (b) and volleys of new (d) waves are observed. The over-all amplitude of the cerebellar activity is 80–100 microvolts.

9. Different results obtained from animals subjected to surgical intercollicular section and animals subjected to the same kind of decerebration, but performed by suction, are attributed to severe injury during suction due to traction on and disruption of fibers to the bulbopontine structures at a much lower level than the point of application of suction. In this case, fibers inhibitory to bulbopontine structures are interrupted as in the case of postcollicular surgical section. The resulting hyperactivity of these structures induces, as is known, slow high amplitude waves on the cerebellar cortex.

10. Slow cerebellar potentials following direct stimulation or stimulation of the bulbopontine structures in the decerebrated cat have been interpreted as of a convulsive nature; the hypothesis is put forward that the said waves may be better interpreted as the effect of sensory inflow to the cerebellar cortex from sources external to the cerebellum. Some experimental support of this view is given.

REFERENCES

1. Adrian, E. D. – J. Physiol., 1935, *83*, 32 P.
2. Bremer, F. and Bonnet, V. – J. Physiol. (Paris), 1953, *45*, 53–56.
3. Brookhart, J. M., Moruzzi, G., and Snider, R. S. – J. Neurophysiol., 1951, *14*, 181–190.
4. Crepax, P. and Pompeiano, O. – Atti Rend. Acc. Lincei, 1955, *18*, 409–412.
5. Dow, R. S. – J. Physiol. (Lond.), 1938, *94*, 67–89.
6. Gualtierotti, T. and Capraro, V. – Arch. Sci. biol. (Bologna), 1941, *27*, 247–262.
7. Gualtierotti, T., Martini, E., and Marzorati, V. – J. Neurophysiol., 1949, *12*, 363–369.
8. Gualtierotti, T. and Schreiber, B. – In preparation.
9. Martini, E., Gualtierotti, T., and Marzorati, V. – Pflügers Arch. ges. Physiol., 1943, *246*, 585–596.
10. Mollica, A. and Naquet, R. – EEG clin. Neurophysiol., 1953, *5*, 585–587.
11. Moruzzi, G. – EEG clin. Neurophysiol., 1950, *2*, 463–469.
12. Moruzzi, G. – Ann. Rev. Physiol., 1951, *13*, 281–296.
13. Moruzzi, G. – Arch. Fisiol., 1955, *53*, 299–325.
14. Moruzzi, G. – Personal communication, 1955.
15. Nulsen, F. E., Black, S. P. W., and Drake, C. G. – Fed. Proc., 1948, *7*, 86–87.
16. Ten Cate, J. and Wiggers, K. – Arch. neerl. Physiol., 1942, *26*, 423–425.

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AN ANALYSIS OF THE ACTIVATING SYSTEM INCLUDING ITS USE FOR SCREENING ANTIPARKINSON DRUGS‡

HISTORICAL

The name "activating system" is applied to a part of the central nervous system which has been subjected to intensive exploration in recent years. Historically, two different schools of workers have made independent studies of this system. The first, headed by Moruzzi and Magoun,[22] began the attack on the caudad portion, the reticular formation. The second school, including Morison and Dempsey[20, 21] and Jasper,[14] has examined the cephalad or thalamic part, and the latter has given it the name of the diffuse thalamic projections to the cortex. These two parts taken together have been termed the mesodiencephalic activating system[24] but for brevity will be simply called the activating system. The reticular formation refers to a central core of gray matter extending from the spinal cord, through the bulbar, pontine, and mesencephalic areas. Besides centrifugal motor influences exerted on the somatic musculature, the reticular formation also possesses centripetal actions.

Bremer[3, 4] observed that the alert electroencephalogram, consisting of low voltage high frequency waves, failed to appear in the cerveau isolé, a brain sectioned through the rostral portion of the mesencephalon and therefore excluding most sensory impulses. This preparation exhibited an EEG pattern of rest or sleep, large slow waves interrupted by spindles of 14 per second frequencies, even though it was capable of receiving some afferent stimuli, for example, visual and olfactory ones. The alert EEG reaction is a function of the activating system. The alerting effect on the cerebral cortex takes place by virtue of centripetal impulses passing through the reticular formation to the thalamic diffuse projection system and evoking a reaction which spreads widely over the cerebral cortex. It is apparent, therefore,

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that the reticular formation and the diffuse projection system together constitute a multineuronal pathway which serves as a functional unit. Impulses from the reticular formation also travel by way of collaterals to the hypothalamus and thence to the cortex either directly or via the thalamus.[17, 20] Thus the hypothalamus is included in the activating reaction.[21]

In a way this activating system may be regarded as being parallel to the specific one which carries impulses from the sensory receptors via the lemnisci to the specific relay nuclei of the thalamus and then to the areas of the cerebral cortex occupied by the analyzers of the specific sensations. This broadly defined physiological entity, the activating system, which has also been delimited anatomically, calls for additional exploration and our own work consists of a pharmacological analysis of the functions of this region.

PREVIOUS INVESTIGATIONS

When we started our investigations we knew that acetylcholine,[1] diisopropyl fluorophosphate (DFP),[2] physostigmine,[10] and tetraethylpyrophosphate (TEPP)[11, 12] produce the alerting type of EEG while atropine[10, 13, 14] evokes the sleep pattern. Our experimental set up was designed to follow the lead afforded by the effects of these cholinergic and anticholinergic drugs. For our studies we used four pairs of coaxial electrodes inserted bilaterally into the brain of a rabbit. We were thus able to record simultaneously from both motor cortices, both limbic cortices, the head of each caudate nucleus, and the medial nucleus of each thalamus. By this method widespread effects of activation were revealed. In addition, we inserted a bipolar electrode into the reticular formation at the level of the superior colliculus. The latter was used especially to stimulate the reticular formation.

In chronological order it was observed first that the injection of acetylcholine into a common carotid of a rabbit evoked an ephemeral alerting response.[9] Next, DFP, a substance which inactivates cholinesterase and permits the accumulation of acetylcholine, produced an electrical picture similar to that of acetylcholine except that it was enduring.[9] Atropine, on the other hand, stopped the alerting effect of both of these drugs and in addition blocked the alerting reaction otherwise caused by such physiological stimuli as pain. These experiments indicate that the activating system is cholinergic in function.[9]

When the reticular formation was stimulated directly by an electrode inserted into it at the level of the superior colliculus we observed the strongest activation and yet this, too, could be prevented by the use of atropine.[9] Further work gave added support for the idea that the part of

the brain most sensitive to cholinergic and anticholinergic drugs is the activating system. In these experiments the left cerebral hemisphere was separated from its neural connections with the rest of the brain by a section through the corpus callosum, anterior commissure, fornix, and internal capsule. The section went lateral to the thalamus but cut through the medial part of the corpus striatum. This isolated left hemisphere, however, retained its major blood supply, while Figure 1 shows that the separated hemisphere

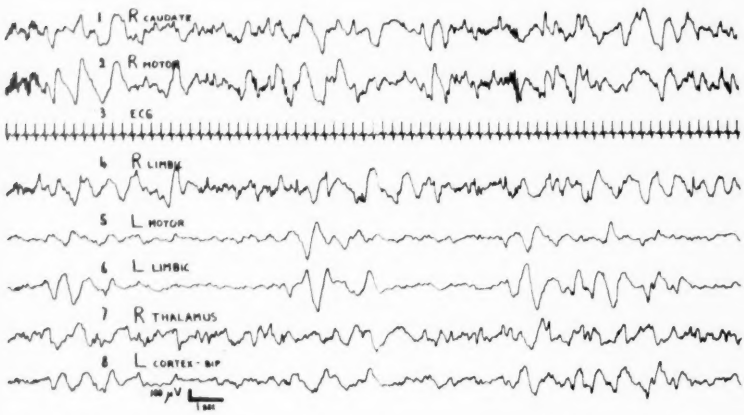

FIG. 1. Isolated hemisphere preparation. The connections of the left hemisphere with the rest of the brain were severed 30 minutes before this record was taken.

Leads as indicated in figure.

The rabbit was kept undisturbed, and the electrical activity of the intact parts of the brain shows the sleep pattern: high-voltage (150-300 volts), slow (1 to 3 c/s), waves and spindles of 12 to 14 c/s waves in the motor cortex, in the caudate nucleus, and in the limbic cortex (the spindles are more prominent in the motor cortex); 1 to 3 c/s activity intermixed with 5 to 6 c/s frequencies in the thalamus. In the cortex of isolated hemisphere (leads 5, 6, and 8) only independent random slow activity is present.

exhibited an electrical activity independent from that of the other parts of the brain.[25] The administration of DFP into the carotid artery produced an alerting reaction in all cerebral areas except in the isolated hemisphere though the drug reached that structure via the blood supply (Fig. 2).[25] The electrical pattern of the isolated hemisphere went on practically unaffected by the DFP because it would seem that the lowest threshold for cholinergic stimulation in the brain lies in the activating system.

Even though this system is cholinergic, it can be stimulated by drugs other than cholinergic ones and inhibited by others than atropine-like agents. For example, hypnotic agents like the barbiturates will inhibit the

alerting response,[7] while stimulants of the central nervous system like Meratran will increase it.[8, 9] With these drugs some other modality of the activating system is affected. The cholinergic system is probably involved but only secondarily.

It is a matter of some importance that the new psychopharmacological agents, used to tranquilize disturbed psychotic patients, also possess a locus of action in the activating system.[10] In small or moderate dosage chlorpromazine inhibits the activating system. The same afferent impulse which

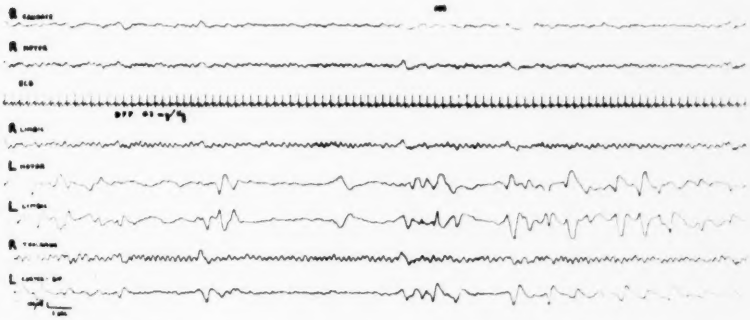

FIG. 2. Same animal as in Figure 1; leads as in Figure 1. After 0.3 mg/kg of di-isopropyl fluorophosphate, i.v. The pattern of alertness is continuous and prominent in the intact parts of the brain. Fast activity at low voltage in the right caudate nucleus and in right motor cortex. In the thalamus and in the right limbic cortex, see the typical 4 to 6 c/s rhythm of thalamic origin. In the cortex of the isolated left hemisphere the random activity continues unmodified, despite the administration of di-isopropyl fluorophosphate.

is successfully recorded in the specific sensory areas at the various levels of the brain no longer evokes the alerting response. The patient, though still aware of his environment, is less affected by it. In contrast, reserpine, even in small doses, facilitates the alerting reaction and brings on an alerting response. This effect on the activating system explains in part the property of reserpine to produce sedation without hypnosis.[7] The same dose which depresses the hypothalamus simultaneously stimulates the alerting reaction so that emotional expression is moderated but sleep is not enforced. Chlorpromazine in large doses also evokes activation[10] and therefore does not enforce sleep. Frenquel, a third drug of this series, does not affect the activating system except under special circumstances.[7] That agent can, however, correct activation when induced by the hallucinogens, D-lysergic acid diethylamide (LSD), and mescaline, but not when the alerting reaction is caused by other drugs, for example, central nervous system stimulants.

TABLE 1. SITE OF ACTION OF ANTIPARKINSON DRUGS

		High voltage slow waves and 14 c/s spindles ← *Depression of the mesodiencephalic activating system*	*Cortical fast low voltage activity and 4-7 c/s thalamic rhythm* → *Stimulation of the mesodiencephalic activating system*
1.	Atropine	++++ 1-10	never
	Artane	+++ 1-5	+ over 10-20
2.	Parpanit	+++ 1-5	+ over 10-15
	Benadryl	+++ 1-8	+ over 10-20
	Diparcol	++ 2-8	++ over 12-20
3.	Lergigan	++ 2-8	++ over 12-20
	Chlorpromazine	++ 2-10	++ over 12-18
	Trasentine	++ 1-10	large amounts
4.	Mephenesin	+ 30-40	++ over 40-60
5.	Trimeton	+ 1-3	++ over 3-4
	Chlortrimeton	+ 1-3	++ over 3-4
	Pyribenzamine		++ 1-6
	Reserpine		+++ 0.5-2
6.	Amphetamine		+++ 1-10
	Nicotine		+++ 0.1-0.2 and convulsions
	DFP		++++ 0.1-0.2

Table illustrating the type and degree of action of drugs upon the mesodiencephalic activating system. The figures represent ranges of dosage in mg./kg. The number of plus signs indicates the intensity of action.

The ability to stimulate the activating system is a part of the functional pathology of the tremor occasionally seen with the new psychopharmacological agents. Obviously atropine or an atropine-like substance which paralyzes the activating system can be used to stop this tremor. In fact, the stimulated reticular formation can be used as a screening mechanism to determine drugs which affect parkinsonism favorably; the following table has been drawn up on this basis (Table 1). You will observe that atropine stands first in this table and Benadryl is also high on the list.[9] We have

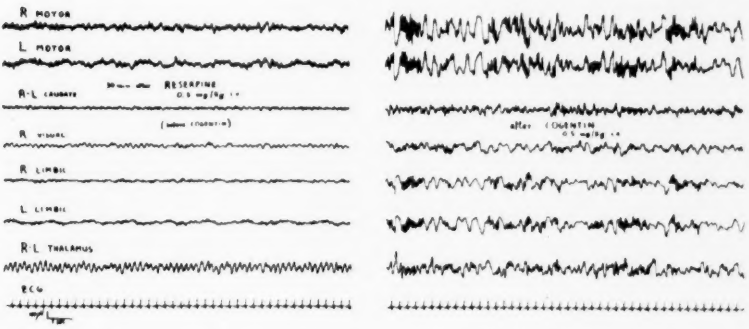

FIG. 3. Left portion of figure illustrates EEG activation caused by reserpine, 0.3 mg./kg. Right part of figure reveals results of injection of Cogentin, 0.5 mg./kg., which restores the sleep pattern in the same animal.

suggested the ability to depress the activating system as a test for antiparkinson drugs and we have been furnished with a test case by a new antiparkinson drug, Cogentin, an agent which partakes of the chemical constitution of atropine, as well as that of Benadryl. Tanaka and Edwards[10] report its successful use in patients with moderately severe symptoms. Cogentin in combination with Benadryl or Rebellon was effective for all of the patients of these observers. Dosbay, Constable, and Fromer[11] found Cogentin highly useful, and in 13 of 20 patients obtained better results from it than from other antiparkinson drugs, with relief of severe tremor. The side reactions are similar to those of atropine like drugs—mydriasis and dry mouth. When the patients became listless the authors obtained better results by combining Cogentin with Artane, since the latter is more stimulant in action than Cogentin. Clinical results of such an order call for further exploration of this apparently important drug and we therefore examined its effects on the activating system of the rabbit.

NEW EXPERIMENTS

Cogentin is potent in preventing excessive activity of the reticular formation. We found that Cogentin reversed the activation caused by reserpine as well as that by large doses of chlorpromazine (Figures 3 and 4). This observation is especially pertinent because Cogentin has been

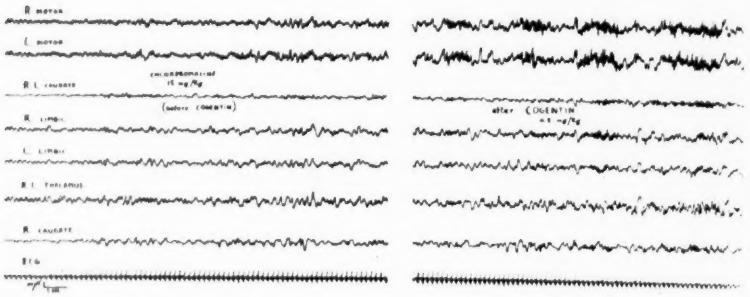

FIG. 4. The stimulating effect of chlorpromazine, 15 mg./kg., which eliminates the sleep spindles, is seen on the left side of the figure. The right side illustrates the restoration of the features of sleep caused by the administration of Cogentin, 0.5 mg./kg.

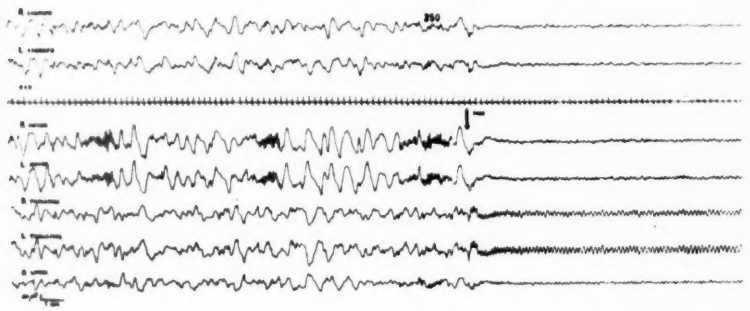

FIG. 5. The effect of pain on the electrical tracings is seen. The pain stimulus is indicated by the arrow.

found efficacious in the Parkinsonism which is a side reaction of reserpine and of chlorpromazine therapy.[12,13,15]

The alerting reaction associated with a painful stimulation (Fig. 5) is eliminated by Cogentin (Fig. 6). Cogentin, likewise, also proved successful against the two most severe tests — the activation of the reticular formation due to the injection of DFP (Fig. 7) and also against the direct electrical stimulation of the activating system (Fig. 8). In both instances the alerting

response could be prevented, or, if allowed to take place, was corrected by Cogentin. This drug is even more potent than atropine, which up to the present was the best depressant of the activating system, for on a weight basis it required less Cogentin than atropine to produce equally good results.

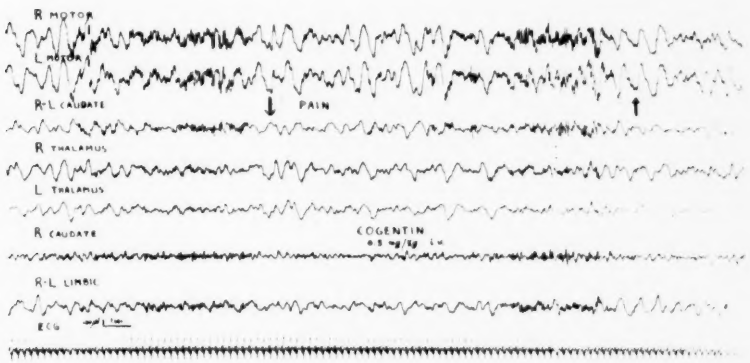

FIG. 6. Failure of a painful stimulus to evoke the alerting reaction is due to the previous administration of Cogentin, 0.5 mg./kg.

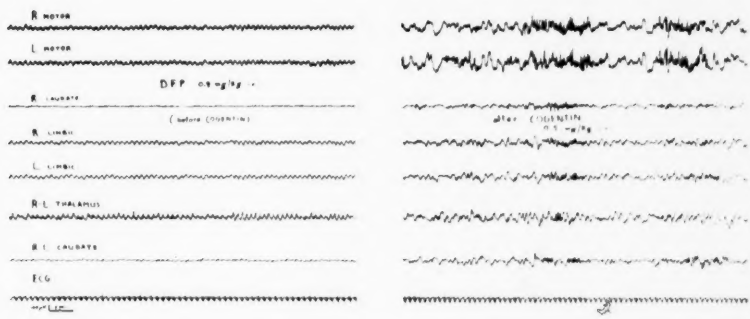

FIG. 7. In the left group of tracings is disclosed an enduring alerting reaction produced by DFP, an effect entirely eliminated by the injection of 0.5 mg./kg. of Cogentin which restores the features of sleep in the tracings on the right portion of the figure.

DISCUSSION

What do these results obtained with Cogentin mean? In this case we are interested not only in the centripetal effects of the alerting system, but also in the centrifugal ones.[7] It would seem that the alerting system and especially its caudad portion, the reticular formation, contains the main extra

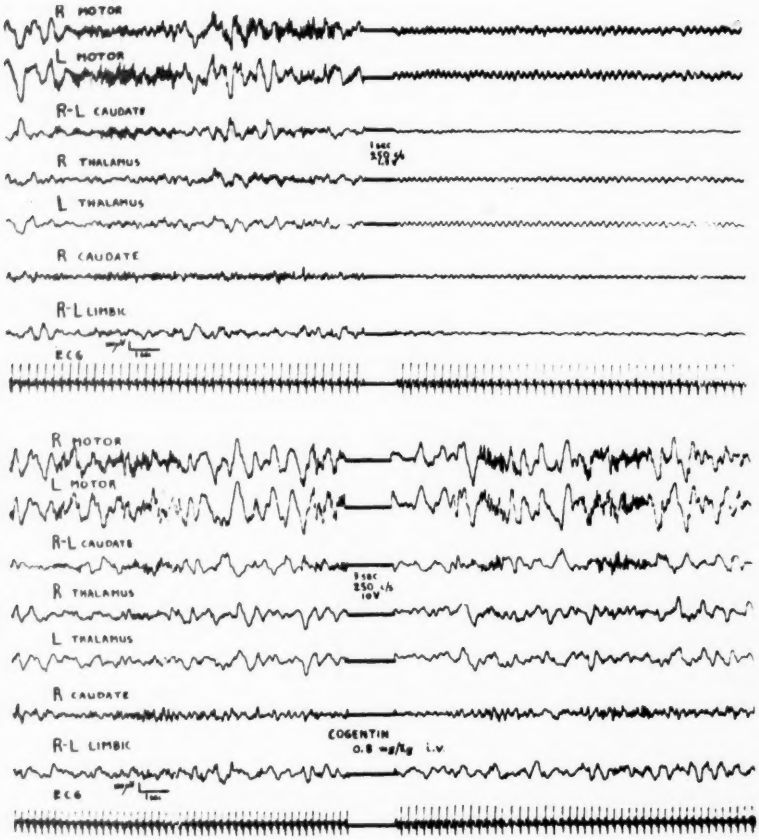

FIG. 8. The upper group of tracings shows strong activation following direct electrical stimulation of the midbrain portion of the reticular formation for one second with 250 pulses per second at 1.5 volts. The lower group of tracings reveals that even stronger stimulation for a longer time, 3 seconds with 250 pulses per second at 10 volts, fails to evoke the alerting reaction after the administration of Cogentin, 0.8 mg./kg.

pyramidal motor tract from the cerebral centers to the anterior horn cells of the cord and thus affects motor activity.

In general, rhythmic alternating tremors have been produced experimentally by two different methods. The first consists of destructive lesions. These have been placed in the mesencephalic tegmentum,[9] and in the reticular formation.[10] The second method is that of electrical stimulation of

the reticular formation.[7] It would seem that the tremor is due to overactivity of the reticular formation, an efferent of the extrapyramidal motor system. In fact, Folkerts and Spiegel[8] suggest that the tremor of Parkinsonism is due to a lesion of the substantia nigra and the subsequent release of the reticular formation from inhibition. Thus, overactivity and disordered function of the reticular formation are induced either by its electrical stimulation or its release from more cephalad structures. Jenkner and Ward[9] also point out that as a result of deafferentiation the reticular formation may become hypersensitive to acetylcholine and respond to the locally produced acetylcholine in an exaggerated and uncoordinated manner.

Finally, it must be emphasized that the results obtained with Cogentin are similar in principle to those of other efficacious antiparkinson compounds, namely, they are achieved by paralysis of the activating system. But the salutary effect consists in more than smoother motor function, important as that is. It is well known that subjective improvement is almost always greater than objective improvement.[10] Our results show that the objective reaction does not depend exclusively on the reaction of the patient to kindly and thoughtful attention. The paralysis of the activating system blocks its cephalad functions. Thus the patient's brain is bombarded by fewer impulses. Even though those from the special senses are still active, the additional background supplied by the alerting system is eliminated. The ability of Cogentin to prevent the arousal reaction to pain is illustrated in Figure 7, but probably most stimuli, including proprioceptive ones from muscle, receive the same treatment. It would seem that the patient's subjective reaction is changed for the better because he undergoes a kind of pharmacological lobotomy.

SUMMARY

In our pharmacological analysis we have found that the activating system is cholinergic in function and is the site in the brain most sensitive to cholinergic and anticholinergic drugs. Because of the part the activating system plays in the functional pathology of Parkinsonism, that system may be used experimentally in animals to screen antiparkinson drugs. Cogentin, a new drug of this type, was found to depress profoundly the activating system. Many other drugs, neither cholinergic nor anticholinergic, also affect the activating system in fundamental ways. A part of the effects of depressants like barbiturates and of stimulants like Meratran are achieved by their action on the activating system. Similarly, reserpine and chlorpromazine derive part of their influence on the brain by affecting the activating system. It should be emphasized that whether we refer to the

cephalad alerting response or to the caudad extrapyramidal control of motion, the drug which affects one function also influences the other and in the same manner. Thus, drugs which alert the cortex may also produce a Parkinsonian tremor, while drugs which prevent the alerting reaction correct Parkinsonism. This two-way action may explain not only the beneficial effects on muscular function, but also the subjective feeling of improvement which these drugs bring with them.

We trust that these studies may be an acceptable contribution to the volume written for the celebration of John Fulton's twenty-five years on the Yale faculty. In a way this paper may be regarded as complementary to his work which contains many studies on the effects of drugs on the brain.[8, 9, 17]

REFERENCES

1. Ayd, Frank J., Jr.: Personal communication.
2. Barsa, J. H. and Kline, N. S.: Personal communication.
3. Bonnet, V. and Bremer, F.: Action du potassium, du calcium et de l'acétylcholine sur les activités électriques spontanées et provoquées, de l'écorce cérébrale. R. Soc. Biol. (Paris), 1937, *126*, 1271-1275.
4. Bradley, P. B., Cerquiglini, S., and Elkes, J.: Some effects of di-isopropyl fluorophosphate on the electrical activity of the brain of the cat. J. Physiol. (Lond.), 1953, *121*, 51P-52P.
5. Bremer, F.: Etude oscillographique des réponses sensorielles de l'aire acoustique cortical chez le chat. Arch. int. physiol., 1943, *53*, 53-103.
6. Doshay, L. J., Constable, K., and Fromer, S.: Preliminary study of a new anti-parkinson agent. Neurology, 1952, *2*, 233-243.
7. Folkerts, J. and Spiegel, E.: Tremor on stimulation of the midbrain tegmentum. Confin. neurol. (Basel), 1953, *13*, 193.
8. Fulton, J. F. and Keller, A. D.: Observations on the response of the same chimpanzee to dial, amytal and nembutal, used as surgical anaesthetics. Surg. Gyn. Obst., 1952, *54*, 764-770.
9. Fulton, J. F., Liddell, E. G. T., and Rioch, D. McK.: The influence of unilateral destruction of the vestibular nuclei upon posture and the knee-jerk. Brain, 1930, *53*, 327-343.
10. Funderburk, W. H. and Case, T. J.: Effect of atropine on cortical potentials. EEG clin. Neurophysiol., 1951, *3*, 213-233.
11. Gellhorn, E.: *Physiological foundations of neurology and psychiatry*. Minneapolis, University of Minnesota Press, 1953.
12. Goldman, Douglas: Personal communication.
13. Grob, D. and Harvey, A. M.: Observations on the effects of tetraethylpyrophosphate (TEPP) in man, and on its use in the treatment of myasthenia gravis. Bull. Johns Hopkins Hosp., 1949, *84*, 532-567.
14. Jasper, H. H.: Diffuse projection system: the integrative action of the thalamic reticular system. EEG clin. Neurophysiol., 1949, *1*, 405-419.
15. Jenkner, J. L. and Ward, A. A., Jr.: Bulbar reticular formation and tremor. Arch. Neurol. Psychiat. (Chicago), 1953, *70*, 489-502.
16. Journal of the American Medical Association. Editorial: Treatment of paralysis agitans. 1955, *157*, 597.

17. Keller, A. D. and Fulton, J. F.: The action of anesthetic drugs on the motor cortex of monkeys. Amer. J. Physiol., 1931, *97*, 537.

18. Kinross-Wright, Vernon: Personal communication.

19. Magoun, H. W.: Caudal and cephalic influences on the brainstem reticular formation. Physiol. Rev., 1950, *30*, 459-474.

20. Morison, R. S. and Dempsey, E. W.: A study of thalamo-cortical relations. Amer. J. Physiol., 1942, *135*, 281-292.

21. Morison, R. S. and Dempsey, E. W.: Mechanism of thalamo-cortical augmentation and repetition. Amer. J. Physiol., 1943, *138*, 297-308.

22. Moruzzi, G. and Magoun, H. W.: Brainstem reticular formation and activation of the EEG. EEG clin. Neurophysiol., 1949, *1*, 455-473.

23. Pscheidt, G. R. and Stone, W. E.: Chemical and electrographic changes produced in the brain by teraethylpyrophosphate. EEG clin. Neurophysiol., 1953, *5*, 126.

24. Rinaldi, F. and Himwich, H. E.: Drugs affecting psychotic behavior and the function of the mesodiencephalic activating system. Dis. nerv. Sys., 1955, *16*, 3-11.

25. Rinaldi, F. and Himwich, H. E.: Cholinergic mechanism involved in function of mesodiencephalic activating system. Arch. Neurol. Psychiat. (Chicago), 1955, *73*, 396-402.

26. Rinaldi, F. and Himwich, H. E.: Alerting responses and actions of atropine and cholinergic drugs. Arch. Neurol. Psychiat. (Chicago), 1955, *73*, 387-395.

27. Rinaldi, F. and Himwich, H. E.: A comparison of effects of Reserpine and some barbiturates on the electrical activity of cortical and subcortical structures of the brain of rabbits. Ann. Acad. Sci., 1955, *61*, 27-35.

28. Rinaldi, F. and Himwich, H. E.: Frenquel corrects certain cerebral electrographic changes. Science, 1955, *122*, 198-199.

29. Rinaldi, F. and Himwich, H. E.: The site of action of antiparkinson drugs. Confin. neurol. (Basel). (In press)

30. Schut, J. W. and Himwich, H. E.: The effect of Meratran on twenty-five institutionalized patients. Amer. J. Psychiat., 1955, *111*, 837-840.

31. Starzl, T. E., Taylor, C. W., and Magoun, H. W.: Collateral afferent excitation of reticular formation of brain stem. J. Neurophysiol., 1951, *14*, 461-477.

32. Tanaka, G. M. and Edwards, J. C.: Treatment of parkinson's syndrome with tropine benzohydryl ether methane sulfonate and other drugs. J. Gerontol., 1952, *7*, 405-409.

33. Vernier, V. G. and Unna, K. R.: Effect of stimulant drugs on tremor monkeys. J. Pharmacol., 1954, *110*, 50.

34. Ward, A. A., Jr., McCulloch, W. S., and Magoun, H. W.: Production of an alternating tremor at rest in monkeys. J. Neurophysiol., 1948, *11*, 317-330.

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PILGRIMAGE TO A SCIENTIFIC SHRINE

In the summer of 1954 my wife and I enjoyed a long-deferred European holiday which included a motor trip in central France. We hired a small Citroen, and M., being more adaptable than I, soon mastered the technique of shifting gears on the dashboard and did all the driving. Arriving in Clermont-Ferrand one afternoon and learning that there was a motor road up a nearby mountain, the Puy de Dôme, I insisted that we drive up to the summit. On the narrow mountain road we had some difficulty in passing a few stalled cars, but our car completed the climb without damage, although a good deal of water boiled out of the radiator. Fortunately this could be replaced from a pitcher borrowed in the mountain restaurant. Knowing that I have long enjoyed hill climbing, M. did not suspect that I had any particular interest in this mountain until we walked to the summit and came upon a bronze tablet with an inscription something like this:

EXPÉRIENCE DE PASCAL.
PESANTEUR DE L'AIR
19 SEPTEMBRE 1648

This was the famous experiment which first showed the influence of altitude on barometric pressure. It was found, as Pascal had expected, that the barometric height was definitely lower on the mountain top than in the city below. Pascal pointed out that the experiment proved that the mercury in a barometer tube is held up by the weight and pressure of the air, and not because nature abhors a vacuum. He also recognized that similar observations could be used to compare the altitudes of different places on the earth, even if they were Antipodes.

The experiment was suggested by Pascal in 1647 in a letter to his brother in-law, Périer, who lived in Clermont-Ferrand. Périer, accompanied by several important men of that city, made the ascent and the observations in the following year. His account of the experiment, in a letter to Pascal, makes fascinating reading.[1,2] Périer seems to have been really thrilled by obtaining exactly the same result on meticulously repeating

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the filling and reading of the barometer in different places on the summit of the mountain, "tantost à couvert dans la petite Chapelle qui y est, tantost à découvert, tantost à l'abry, tantost au vent, tantost en beau temps, tantost pendant la pluye & les brouillards . . ." That I, too, was thrilled by going to this spot is a tribute to the influence of J.F.F.

REFERENCES

1. Pascal, (B.): *Traitez de l'equilibre des liqueurs, et de la pesanteur de la masse de l'air*. Paris, G. Desprez, 1663, pp. 176-188.
2. Magie, W. F.: *A source book in physics*. New York, McGraw-Hill Book Company, 1935, pp. 73-75.

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RUPTURED THORACIC DISCS

During the eighteen months immediately prior to this report the authors have seen five cases of typical ruptured thoracic intervertebral discs. These have been studied, treated by surgery, and the results, in contrast to some previous reports,[1] have been sufficiently gratifying that it is felt they should be reported.

There are a few characteristic features which may be found of interest in ruptured discs in this particular area. As in those in the cervical area, they may be divided into two distinct classes—(i) those producing cord pressure with long tract signs, and (ii) those more laterally placed, producing root pressure with typical radicular signs and symptoms. In retrospect it is felt that other cases have probably been overlooked by the authors, particularly those cases showing the lateral protrusion with radicular signs. In two such cases suggestive myelographic defects have been found, but conservative management resulted in eventual improvement after a protracted period of incapacity. It seems quite probable that the incidence is greater than may be indicated in this and previously reported series and, as has been emphasized,[1] occasional instances of cryptic thoracic and abdominal pain might be explained on the basis of such pathology.

CASE REPORTS

The first two of the following case reports are those in which the size and location of the ruptured disc fragment were such as to produce cord compression with signs and symptoms of long tract involvement.

Case 1. (Progressive severe long tract signs, simulating a cord neoplasm, with no trauma; marked improvement following removal of disc.)

E.F., a 43-year-old man, was admitted to the Newington Veterans Administration Hospital in April, 1955, complaining of difficulty in maintaining balance with a

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tendency to veer to the left. He suffered from impotence. He noted low back pain with radiation into both legs. Numbness was present in the left lower extremity. Symptoms were of two months' duration and were not preceded by trauma. He denied radicular thoracic pain.

Physical examination revealed paraspinal spasm in the lumbar region with a list to the right. There was atrophy of the left thigh and calf. The left lower extremity was weak in all muscle groups. Deep reflexes in the lower extremities were markedly hyperactive with unsustained ankle clonus. Vibratory and position sense in the feet were impaired. Abdominal reflexes were absent. There was a positive Babinski on the left. During his preoperative course positive Babinskis appeared bilaterally. He was very ataxic and this became progressively disabling so that walking was not possible unassisted.

X-rays of the spine revealed first-degree lumbosacral spondylolisthesis. There were only eleven thoracic vertebrae. A myelogram revealed a complete block at D9-10 (Fig. 1). Cerebrospinal fluid protein was 155 mg %.

Operation (NHH & BBW): On June 10, 1955 a laminectomy was performed with removal of a soft, free-lying disc fragment extruded from the D9-10 interspace. Intradurally no neoplasm was noted.

Postoperative course: The patient was greatly improved following surgery. One month postoperatively he exhibited only slight weakness of the left foot. All sensory deficit disappeared. There was minimal pain in the left hip. Babinskis reverted to normal. Hyperactive reflexes persisted. The gait was normal.

Case 2. (Concomitant cervical and thoracic discs with long tract signs persisting until removal of the latter.)

G.D., a 49-year-old man, was admitted to the Neurosurgical Service at the Hartford Hospital for the first time in April, 1953, complaining of paresthesias in both hands, in the interscapular area, and in the left lower extremity. He dated his symptoms from sudden snapping back of his head, occurring fifteen months before when a bus in which he was a passenger stopped suddenly. Pains were intermittent in character. He also complained of increasing impotence. The only positive physical findings were discomfort and pain elicited by hyperextension of the neck, the patient experiencing paresthesias in both hands and down the left lower extremity.

X-rays of the cervical spine were normal. A cervical myelogram revealed a central filling defect at the C3-4 interspace and a persistent defect on the left at the D11-12 interspace. Cerebrospinal fluid protein was 62 mg %.

Operation (BBW): On May 12, 1953 a cervical laminectomy was performed. No intradural pathology was found. An extradural mass was felt anteriorly and proved to be a soft disc fragment lying free in the spinal canal. A hole in the annulus at the C3-4 interspace was found. The fragment was removed.

Postoperative course: Symptoms in the upper extremities disappeared. The patient had some difficulty in starting his urinary stream. A transurethral resection was done to correct a bladder neck obstruction.

The patient was readmitted in November, 1953, with complaints of burning paresthesias in both lower extremities, worse on the left. These paresthesias extended as high as the midabdomen and were aggravated by trunk flexion. Hesitancy in starting his urinary stream persisted. Repeat myelogram performed during a brief

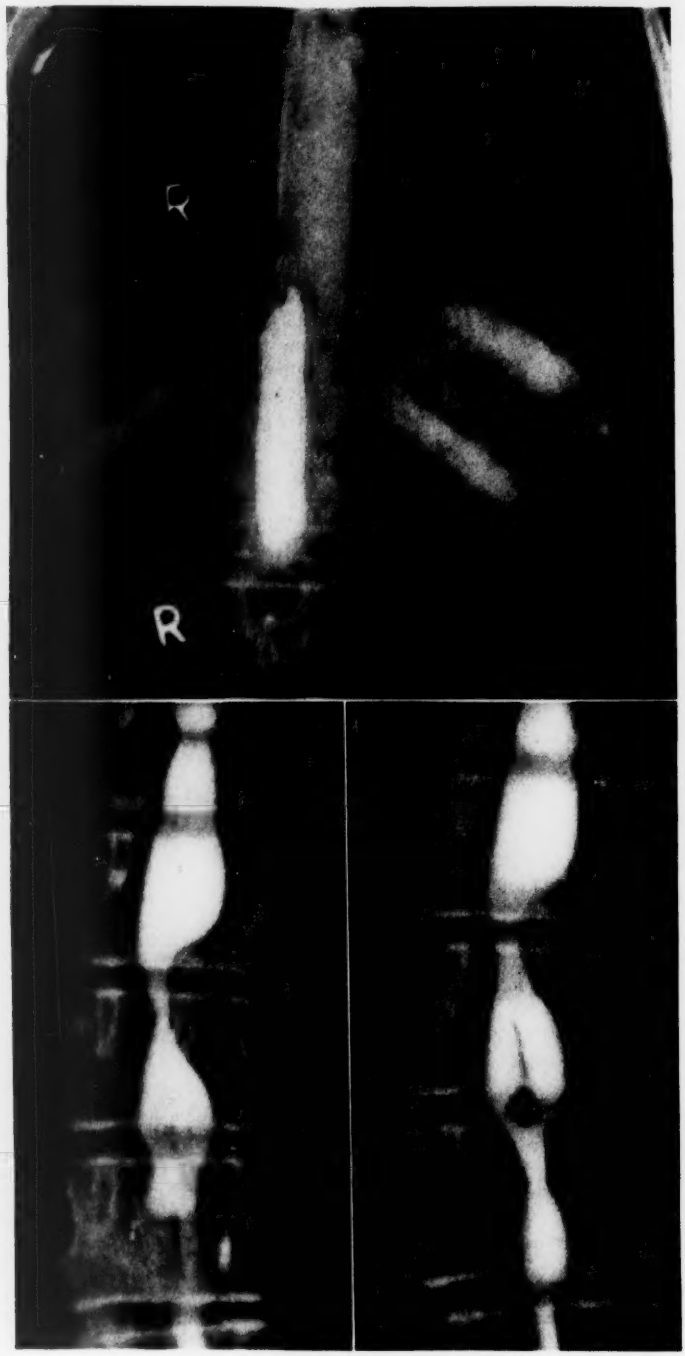

FIG. 1. Case 1. A-P thoracic myelogram showing complete block at D9-10. (There were only 11 thoracic vertebrae.)

FIG. 2. Case 3. A-P thoracic myelogram showing persistent meniscoid defect at D7-8, right, in two different exposures.

interval admission had shown the same D11-12 defect on the left, demonstrated in the original myelogram. Cerebrospinal fluid protein was 57 mg.%.

Physical examination revealed tenderness on pressure over the D11 spinous process. Reflexes in the lower extremities were hyperactive. No pathological reflexes were present. Abdominal reflexes were absent on the left.

Operation (BBW): On December 2, 1953 a thoracic laminectomy was performed. The dura was opened but no intradural pathology was evident. An anterior extradural bulge was investigated and found to be a soft free disc fragment extruded from the D11-12 interspace. This was removed.

Postoperative course: Eighteen months after surgery the patient experienced persistent paresthesias in the left lower extremity on sitting, but this disappeared at work during which he stands, fully employed as a machinist. The impotence has disappeared. Deep tendon reflexes in the left lower extremity were still hyperactive.

The remaining three cases are those where the ruptured disc fragments were laterally placed, producing root compression with radicular signs and symptoms, pain being the presenting symptom in all.

Case 3. (Previous history suggestive of lumbar and cervical disc disease; radicular pain relieved by disc removal.)

G.C., a 25-year-old female, was seen originally in 1949 for radicular pains in the upper and lower extremities which suggested a discogenic origin. They subsided without treatment. In 1953 she had a brief attack of pain in the right thorax which subsided spontaneously. Neurological examination was negative. In June, 1955, she was admitted to the Hartford Hospital four days after experiencing sharp pain radiating into the right lower thorax and right upper quadrant. It occurred after heavy lifting and was exaggerated by deep breathing and coughing.

Physical examination revealed tenderness on percussion over the D7 spinous process. There was moderate scoliosis with concavity to the right in the dorsal region. There was sensory deficit over the D7 dermatome on the right (Fig. 3). The right upper abdominal reflex was absent. Lateral flexion of the spine increased pain.

X-rays of the spine revealed narrowing of the D7-8 interspace. A myelogram revealed a persistent filling defect at the D7-8 interspace on the right (Fig. 2). Cerebrospinal fluid protein was 70 mg.%.

Operation (FGR): On June 27, 1955 a free disc fragment was found compressing the D7 root, having been extruded from the D7-8 interspace. The dura was not opened.

Postoperative course: Three weeks postoperatively the patient was pain free. Hypalgesia over the D7 dermatome persisted. She showed almost complete recovery in six weeks.

Case 4. (Unilateral radicular pain in the thorax, relieved by disc removal and posterior rhizotomy.)

C.W., a 36-year-old jet pilot, was admitted to the 3700th U.S.A.F. Hospital in March, 1954, complaining of pain in the thoracic spine. The pain radiated anteriorly to the left upper quadrant. It was aggravated by sitting, wearing a parachute, and during aerial maneuvers in which several times the force of gravity was exerted on the pilot.

It was insidious in onset and lasted four months. The only positive physical finding was aggravation of thoracic pain by marked flexion of the neck.

X-rays of the spine revealed calcification in the D9-10 intervertebral disc. A myelogram revealed a persistent filling defect at the D9-10 interspace on the left. Cerebro-

FIG. 3. Case 3. Maximal area of detectable hypesthesia.

spinal fluid protein was 80 mg.%. An electromyogram revealed evidence of nerve root irritation at the D9 root level in the erector spinae group of muscles on the left.

Operation (Kenneth J. Richland and NHH): On April 8, 1955 a dorsal laminectomy was performed. A large, soft bulge elevated the D9 root on the left. Incision into the mass revealed degenerated disc material with gritty calcium deposits. Microscopic

examination confirmed the gross impression. Intradural examination was normal. A dorsal rhizotomy of D9 was done to assure relief of pain.

Postoperative course: An excellent result was obtained. Three months postoperatively he was still pain free and had returned to duty.

Case 5. (Radicular pain associated with Horner's syndrome, relieved by disc removal.)

B.J., a 43-year-old woman, was admitted to the Hartford Hospital in July, 1954, with a story of severe right shoulder pain for ten days extending down the medial aspect of the arm and into the chest. There was no antecedent trauma.

Physical examination revealed a typical Horner's syndrome on the right and hypalgesia over D1 and D2 dermatomes on that side. In addition, neck motions were restricted and produced pain.

X-rays of the cervical spine and chest were normal. A cervical myelogram revealed a persistent filling defect at the D1-2 interspace on the right. Cerebrospinal fluid protein was 49 mg %.

Operation (BBW): On July 24, 1954 a free disc fragment was found under the D1 root on the right extruded from the D1-2 interspace.

Postoperative course: The patient did well symptomatically. Shoulder, arm, and chest pain disappeared. When seen in June, 1955, approximately one year after surgery, there was a residual Horner's syndrome still present on the right.

DISCUSSION

In this group of cases there are two features that are consistently present: (1) The myelogram was positive in all cases, and (2) there was definite elevation of protein content in the spinal fluid, the average elevation being greater than that usually seen in lumbar or cervical ruptured discs. The age group is quite typical of that seen in ruptured discs in other locations, the youngest being 25 and the oldest, 50. Although a preponderance of males has been reported,[7] no sex variation appeared in our small group of patients.

A definite history of trauma was present in two cases (Cases 2 and 3), while trauma was probable in Case 4 where the patient, a pilot, had been exposed to a force several times that of gravity in his flying maneuvers. The symptoms in those cases having the picture of nerve root compression were similar in all, being essentially pain over the distribution of the involved nerve root. Although this presenting symptom could be altered frequently by certain dynamics of the spine, the association with dynamics is much less noticeable in the ruptured disc of the thoracic region than in those of the more mobile lumbar or cervical spine. Indeed, the nature of the pain is such that functional features have been suspected. In Case 5 the radiation of pain was into the arm and, although anatomically it was a ruptured disc in the thoracic region, clinically it appeared to be more closely allied with a ruptured cervical disc. Symptoms in those two cases showing long tract signs were more varied; however, both cases complained of paresthesias, weak-

ness, and impotence. Case 2 presents two complicating features which require some explanation: first, the urinary sphincter difficulty was not corrected by operative removal of local bladder neck pathology. Only after the thoracic disc removal did significant improvement result. Secondly, the concomitant presence of a ruptured cervical disc poses the question of its significance in the production of the long tract signs. The upper extremity symptoms disappeared after the cervical disc removal, whereas those in the lower extremities persisted. Since the reflex changes and paresthesias in the lower extremities still persisted despite removal of the thoracic disc, it is difficult to be certain which of the two lesions was responsible; however, improvement in regard to the bladder symptoms and impotence did not occur until the thoracic disc was removed.

Physical signs demonstrated local tenderness and muscle spasm in three instances, pain on forward flexion in four cases, pain on rotation and lateral flexion in only one case, and Lhermitte's phenomenon in two cases.

The only thing seen in the routine x-rays of the thoracic spine was a thinning of the disc space in one and calcification within the disc in another. Calcification has been reported in eight of eleven cases.[2] A recent series reported elevation of spinal fluid protein in only one case.[1] In contrast, all of the above cases showed protein elevation. In discussion of the myelographic findings, one appreciates the obstacles encountered. The difficulty in establishing a lateral defect in thoracic myelography is well known. The importance of taking several exposures as the dye is passing into the suspected area bears emphasis. In each instance of laterally ruptured disc there has been a great consistency in outline of the lateral defect common to the different exposures (see Fig. 2, *a* and *b*). Electromyography was done in only one case, and here there were definite changes indicative of irritative phenomena picked up on the side of the lesion.

As to location of the ruptured discs in this series, one was at D1-2, one at D7-8, two at D9-10, and one at D11-12. In reviewing the location of lesions in three other series,[2,3,5] no area appears to be immune, but the lower third of the thoracic spine is affected with greatest frequency. To our knowledge no previous published report of a D1-2 disc has been made. Several cases of D12-L1 discs have not been included in this report because we believed that they could not be classified as thoracic discs in the strict sense.

Preoperative diagnosis in three instances was ruptured intervertebral disc and in two instances—where the long tracts were involved—tumors were felt to be more likely. Multiple sclerosis, herpes zoster, and psychoneurosis were diagnoses also considered in the process of study of these cases.

Surgery. A complete laminectomy was felt to be essential for the centrally ruptured discs, while hemilaminectomy usually was sufficient for those laterally displaced. In every case the ruptured disc fragment was removed. In one instance section of a dorsal root was done as well and in three instances the dura was opened to facilitate the expression of disc fragments without trauma to the cord. The dura was closed in all instances with closure technique not unlike routine procedure for dorsal laminectomy.

Pathologically, there were typical sequestra of fibrocartilage in all cases. In four cases the fragments had ruptured completely through the posterior longitudinal ligament and were lying free in the spinal canal. In one instance there was a large protrusion covered by the posterior longitudinal ligament. This latter, although containing gritty calcification, was soft and degenerated.

Results. In each case the pain has been completely controlled by the procedure. In two cases showing long tract signs, the signs have reverted completely to normal in one and have been markedly improved in the other although he still complains of some paresthesias in one leg. In this instance a ruptured cervical disc had previously been removed, which complicates the results. The reflexes in the lower extremities are slightly hyperactive in both, but the Babinskis have disappeared. The Horner's syndrome in Case 5 has persisted although is less noticeable than at onset.

Although thoracic discs are notoriously uncommon because of the relative immobility of this part of the spine due to support of the rib cage, the authors believe that too frequently proper cognizance is not taken of thoracic root pain; certain negative abdominal explorations and gallbladder studies might possibly be explained on this basis. It might occasionally be revealing to perform myelography of the thoracic spine in instances of unexplained thoracic and abdominal pain before making a diagnosis of psychoneurosis or some functional disorder.

SUMMARY

Five cases of ruptured intervertebral disc in the thoracic region are reported; three cases were associated with root compression with radicular signs and two with cord compression and long tract signs. In each case the defect was shown on pantopaque myelography and the protein content of the spinal fluid was definitely elevated. In each case there was gratifying relief following surgical removal. The possibility of ruptured intervertebral disc of the thoracic region as a cause for unexplained pain in the thorax and abdomen is suggested.

REFERENCES

1. Epstein, J. A.: The syndrome of herniation of the lower thoracic intervertebral discs with nerve root and spinal cord compression. J. Neurosurg., 1954, *11*, 525-538.
2. Logue, V.: Thoracic disc prolapse with spinal cord compression. J. Neurol., Neurosurg. Psych., 1952, *15*, 228-241.
3. Love, J. G. and Keefer, E. J.: Root pain and paraplegia due to protrusions of thoracic intervertebral disks. J. Neurosurg., 1950, *7*, 62-69.
4. Muller, R.: Protrusion of thoracic intervertebral disks with compression of the spinal cord. Acta med. scand., 1951, *139*, 99-104.
5. Young, J. H.: Cervical and thoracic intervertebral disk disease. Med. J. Aust., 1946, *2*, 833-838.

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SUBCORTICAL MECHANISMS IN THE "SEARCHING" OR "ATTENTION" RESPONSE ELICITED BY PREFRONTAL CORTICAL STIMULATION IN UNANESTHETIZED CATS§

In a previous paper the authors have described a characteristic "searching" or "attention" response which can be elicited by electrical stimulation of cortical regions of the medial surface of the hemisphere as well as from the hippocampus of unanesthetized cats.[18] Quite a similar type of response may be obtained on stimulation of the phylogenetically younger basolateral division of the amygdaloid nuclear complex, but not from its phylogenetically older anteromedial part.[17]

The response is a rather typical one (Fig. 1). Immediately at the onset of stimulation all spontaneous pre-occupation such as walking or licking ceases; the facial expression changes to one of "attention," perhaps associated with some surprise, bewilderment, or anxiety: the animal raises its head, the eyes open and the pupils dilate; there are slight pricking movements of the ears and quick anxious glancing or searching movements of the eyes and head, almost invariably to one side, contralateral to that of stimulation. This searching may result in circling movements to the opposite side of that stimulated. The reaction to external stimuli seems to be decreased, the animal's attention being intensely fixed on "something imaginary" in the environment.

In some animals, particularly with low-intensity stimulation, the quick glancing movements were directed towards both sides, sometimes predominantly to the ipsilateral side. By slightly increasing the stimulus intensity, however, the glancing changed to the contralateral side.

In Fig. 2A the filled squares indicate the points on the medial aspect of the hemisphere from which this "searching" or "attention" response has

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been elicited. The responsive sites appear to be located mainly within the prefrontal cortex and the limbic (cingular) gyrus (including the anterior and posterior limbic areas and the retrosplenial region). Finally, some points are located within the medial portion of the hippocampal gyrus.

The present investigation is concerned with the subcortical structures involved in this "searching" response obtained by stimulation of the medial

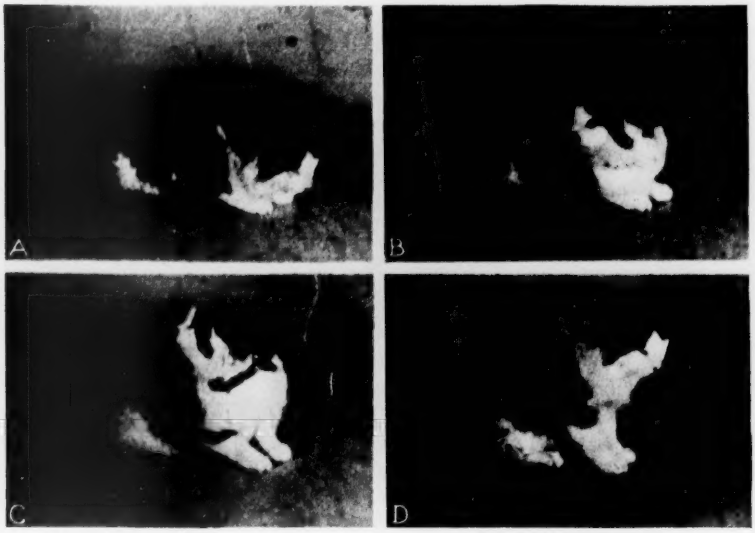

FIG. 1. The "searching" or "attention" response elicted by electrical stimulation of the medial surface of the left prefrontal region. A. Before stimulation. B and C. A few seconds after onset of stimulation; quick glancing movements towards the right side. D. A few seconds after end of stimulation.

prefrontal cortex. The method employed has been to implant needle electrodes in the responsive cortical field and, on the following days, to make various subcortical lesions followed by repeated cortical stimulation. By this combined stimulation ablation technique subcortical structures whose integrity are necessary for the elicitation of the response have been determined.

MATERIAL AND METHODS

In a series of 30 cats a total of 60 bipolar needle electrodes, insulated except for the tips, were implanted in the medial prefrontal areas of cats under Nembutal anesthesia. The following day, when the effect of the anesthesia had worn off, stimulation was carried out while the animal was freely moving on a platform. In the animals yielding

the "searching" response (45 of the 60 electrodes) various subcortical structures were destroyed electrolytically, the electrodes being oriented by the Horsley-Clarke instrument. After a second complete recovery from the anesthesia the prefrontal stimulation was repeated. In some animals in which the subcortical lesion left the prefrontal "searching" response intact, one or two additional lesions were made. After a few days the cats were killed and the sites of the stimulating electrodes and the extent of the subcortical lesions were identified in histological sections. For further details of the method the reader is referred to a previous communication.[18]

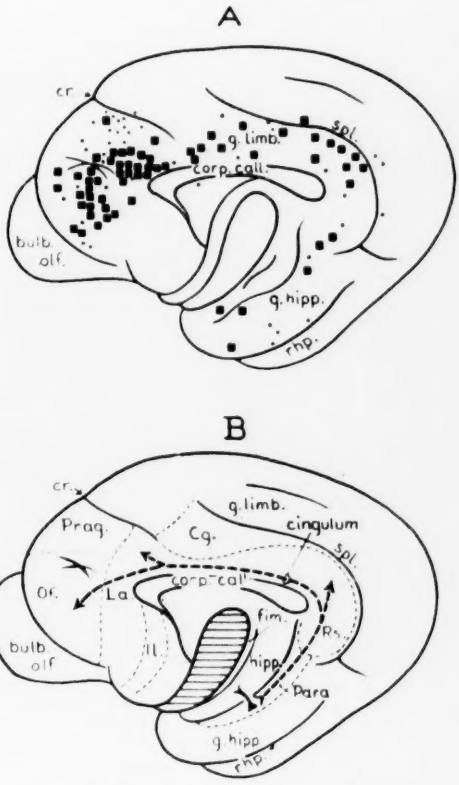

FIG. 2. A. Medial aspect of the cat's hemisphere indicating points (squares) from which the "searching" response has been produced on electrical stimulation. Dots, no such response. B. Area subdivision of the medial surface, mainly according to Rose and Woolsey.[9] Origin and course of the fibers of the cingulum bundle according to current concept (cf. text).

RESULTS

A. Lesions of the cingulum bundle. According to the recent study of Adey and Meyer[1] a conspicuous portion of the cingulum bundle of monkeys originates in the granular prefrontal cortex, mainly from its medial division. Further contributions to the cingulum bundle come from the anterior and posterior limbic (cingular) gyrus. These fibers appear to terminate in the pre- and parasubiculum of the hippocampal formation and possibly in the hippocampus itself.

Because of the similarities between the distribution of the sites yielding the "searching" response, and the origin, course, and termination of the cingulum bundle (Fig. 2) our interest was first focused on this bundle as the possible mediator of the response from the prefrontal region.

However, complete bilateral section of this bundle in four cats at a trans-

verse plane corresponding to the middle or posterior portion of the corpus callosum did not influence the "searching" response elicited from the prefrontal cortex (Fig. 3). The response could be induced just as readily after this section as in the intact animal. In the experiment illustrated in Figure 3, both fornices were included in the lesion, indicating that the prefrontal "searching" response is independent of this structure as well.

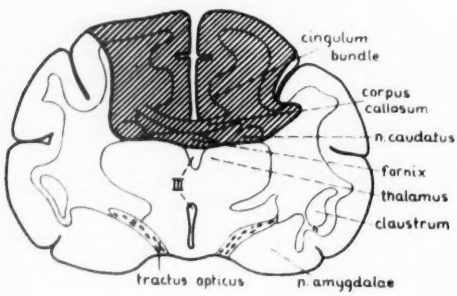

FIG. 3. Diagram of transverse section through an electrolytic lesion severing the cingulum bundle and the fornix on both sides. The "searching" response elicited by stimulating the medial prefrontal cortex on the right side remained entirely unaltered after this lesion.

B. Amygdala, septal nuclei, hypothalamus, stria medullaris, and habenula. Extensive bilateral lesions of these structures were without noticeable influence on the prefrontal "searching" response. The lesions of the amygdala usually included part of the internal capsule (Fig. 4), but in other experiments the amygdala was destroyed more selectively. In one cat the hypothalamic lesion extended from the mammillary bodies posteriorly to the optic chiasma rostrally and included the anterior portion of the posterior hypothalamic nucleus, the greater portion of the dorsal and anterior hypothalamic area, and the ventromedial nucleus, mainly on the ipsilateral side.

C. Thalamus. Following lesions of various parts of the thalamic nuclear complex in 10 cats the prefrontal "searching" response was either eliminated, altered in character, or left intact. Description of a few experiments will best serve as illustration.

Cat 52. Typical contralateral "searching" responses were obtained by stimulating through two electrodes implanted in the medial prefrontal cortex on the *right* side. An extensive lesion was then made of the *ipsilateral* medial half of the thalamus (Fig. 5, right side). The lesion included the stria medullaris and the greater part of the habenula, the entire dorsomedial and most of the anterior nucleus, the medial part of the n. lateralis posterior and n. lateralis anterior, and almost the entire n. centralis medialis, n. paracentralis, and n. centralis lateralis on the same side.

Following this lesion the prefrontal "searching" response was less pronounced and changed in character from a typical contralateral searching to a predominantly ipsilateral response.

A second lesion involving the septal nuclei on both sides had no effect. However, following a third lesion of the medial part of the thalamus on the *left* side the "searching" response elicited from the right prefrontal cortex was completely abolished. This lesion included, as is seen from Figure 5 (left), the stria medullaris, the greater part of the dorsomedial nucleus and of n. centralis medialis, n. paracentralis, and n. centralis lateralis, and, finally, the medial portion of the nuclei lateralis anterior and posterior.

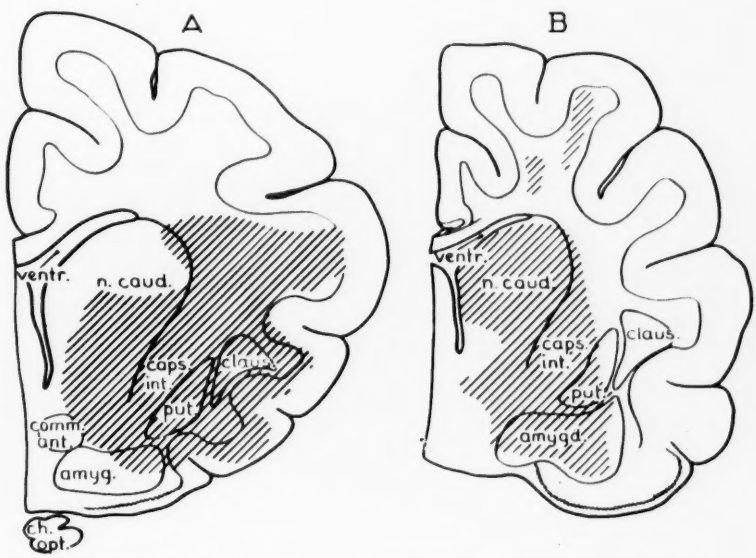

FIG. 4. Diagram of transverse sections through the right hemisphere in two cats with extensive lesions of the internal capsule and adjacent grey nuclear masses (cf. text).

It may be concluded from this experiment that the prefrontal "searching" response is abolished by a bilateral lesion of the medial portion of the thalamus.

Further experiments with smaller lesions of the medial thalamus led to the following generalization: The prefrontal "searching" response disappeared only following lesions of the greater part of the cells of the n. centralis medialis, n. paracentralis, and n. centralis lateralis on both sides. On the other hand, rather extensive lesions of the medial thalamus sparing these nuclei did not significantly influence the response. Thus, the lesion illustrated in Figure 6, leaving the n. centralis medialis, n. paracentralis, and n. centralis lateralis intact, but including on both sides the greater part of the dorsomedial nuclei and habenulae, the medial portion of the nucleus

lateralis posterior and the centrum medianum, and, further, the rostral portion of tectum mesencephali and the peri-aqueductal grey did not alter the prefrontal "searching" response.

From these and a number of similar experiments it was *concluded* that bilateral lesions of the following thalamic nuclei seemed to be of no influence on the prefrontal "searching" response: the lateral, the dorsomedial and the anterior nuclei, the centrum medianum, and the n. reuniens. The same was true for rather extensive lesions of the rostral parts of the tectum mesencephali. *Ipsilateral* lesions of the n. paracentralis and n. centralis lateralis were followed by some reduction of the response and sometimes in a reversal of the searching from the contralateral to the ipsilateral side. On the other hand, lesions of these nuclei confined to the contralateral side appeared to be without any effect.

D. Lesions of the white matter between the prefrontal cortex and the diencephalon. Electrolytic lesions involving the anterior basal portion of the ipsilateral internal capsule just below and lateral to the head of the caudate nucleus in three cats completely abolished the "searching" response which could be readily obtained in these animals pre-operatively on stimulating the prefrontal cortex on the same side (Fig. 4). In these experiments various portions of the neighboring amygdaloid nuclei, caudate, putamen, claustrum, and the fibers of the lateral part of the internal capsule were included in the lesion, but the results obtained in other animals with lesions of these structures permit one to conclude that the "searching" response elicited from the prefrontal cortex is dependent on the fibers running through the anterior basal portion of the internal capsule. This portion, then, most likely contains the fibers interconnecting the medial prefrontal cortex and those thalamic midline nuclei responsible for the stimulation effect.

DISCUSSION

The subcortical structures of importance for the elicitation of the "searching" or "attention" response from the medial prefrontal cortex appear to be the n. centralis medialis, n. paracentralis, and n. centralis lateralis, which are parts of the intralaminar nuclei of the thalamus. It is of considerable interest that Akert,[2] working in Hess' laboratory, has reported briefly on a similar type of behavioral change (consisting of a slow turning of the head to the contralateral side) on stimulating the intralaminar nuclei and of the adjacent dorsomedial and anterior thalamic nuclei. Thus, a cortico-thalamic rather than a cortico-cingulo-hippocampal mechanism seems to be involved. It seems likely, although not yet proven, that the

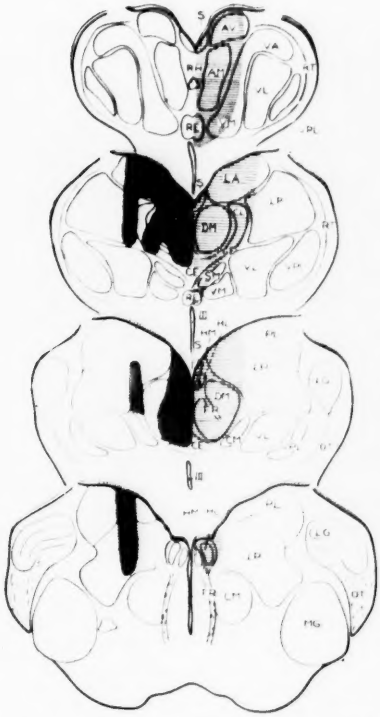

FIG. 5. Drawings of serial sections through two electrolytically produced lesions of the thalamus; the first on the right side (horizontally shaded), the second on the left side (cross-hatched). Cf. text.

FIG. 6. Drawings of serial sections through a rather extensive lesion of the medial thalamus, but sparing the n. centralis medialis (CE), n. paracentralis (PCE), and n. centralis lateralis (CL). This lesion was without any influence on the prefrontal "searching" response.

ABBREVIATIONS FOR FIGURE 5 AND FIGURE 6 (ACCORDING TO JIMENEZ-CASTELLANOS[14])

AM	n. anteromedialis	OT	optic tract
AQ	aqueduct	P	n. posterior
AV	n. anteroventralis	PC	posterior commissure
CE	n. centralis medialis	PCE	n. paracentralis
CL	n. centralis lateralis	PL	pulvinar
CM	n. centrum medianum	RE	n. reuniens
CP	cerebral peduncle	RH	n. rhomboidalis
DM	n. dorsomedialis	RT	n. reticularis
FR	fasciculus retroflexus	S	stria medullaris
HL	n. habenularis lateralis	SM	n. submedius
HM	n. habenularis medialis	SN	substantia nigra
LA	n. lateralis, pars anterior	VA	n. ventralis, pars anterior
LG	lateral geniculate body	VL	n. ventralis, pars lateralis
LP	n. lateralis, pars posterior	VM	n. ventralis, pars medialis
MG	medial geniculate body	VPL	n. ventralis, pars posterolateralis
NR	n. ruber	VPM	n. ventralis, pars posteromedialis

similar type of behavioral response which can be induced from the cortex of the limbic and hippocampal gyri[13] and from the basolateral division of the amygdaloid nuclear complex[12] is dependent on a similar cortico-thalamic and an amygdalo-thalamic mechanism. In this connection it is relevant to recall the recent physiological demonstration of fiber connections from the lateral division of the amygdala to parts of the intralaminar nuclei.[2, 3]

The present study indicates that the medial prefrontal cortex is connected not to the entire—but only to a smaller and limited portion of the intralaminar and midline nuclei of the thalamus. This suggests the possibility of regional localization within these nuclei which one, from a physiological point of view, has been inclined to consider a functional entity with rather diffuse cortical connections.

It may be inferred from the present experiments that the prefrontal cortex exerts a bilateral influence on the central nuclei, more strongly on the ipsilateral than on the contralateral side. This is consistent with the alteration of the typical contralateral searching to an ipsilateral response subsequent to a lesion of the medial thalamus on the side stimulated; the influence on the opposite, intact side of the thalamus now predominates, resulting in a response ipsilateral to the side of cortical stimulation. (It should be recalled that direct stimulation of the intralaminar nuclei results in a contralateral response.) A bilateral lesion of the thalamic nuclei in question is necessary completely to eliminate the effect.

A most conspicuous feature of the "searching" or "attention" response is the initial arrest of all pre-stimulatory activities, the cessation of all movements in execution, including respiration, without any appreciable loss of muscular tone. It is most likely that this quieting effect on movements represents the same phenomenon as that previously observed by Tower[9] in anesthetized cats on stimulating in the medial hemisphere the same cortical areas which are dealt with in this communication. Tower's findings have been confirmed and the inhibitory effects on somato-motor activities studied in greater detail by one of us.[11, 8, 10]

The functional significance of the "searching" or "attention" response is not clear. The term "attention" merely refers to the outward manifestation of the behavior change. Extreme caution must be exercised in any attempt to interpret the real nature of the response. This particularly applies to animal experiments in which we lack any information concerning the animal's subjective experience and level of consciousness during the stimulation. A few suggestions, however, might be ventured:

As discussed previously,[18] we are inclined to consider the "attention" response as secondary to some kind of sensation or physical experience. The animals are undoubtedly conscious, but their attention appears to be

attracted and intensely fixed on "something" which they seem to experience. As a consequence there is frequently an impairment of the animal's usual alertness with decreased reactions to external, visual, auditory, and tactile stimuli. On the other hand, one should not forget that we are dealing with an artificial type of stimulation which might interfere with the normal functioning of the subcortical structures in question.

According to the current concept the intralaminar nuclei are included in the brain stem activating system. They have been shown to yield an arousal effect of the electrocortical activity on high frequency stimulation and have also been considered to increase the animal's general alertness. An immediate inhibition of pre-stimulatory somato-motor activities is also a characteristic of intralaminar stimulation and possibly represents an integrative part of the arousal or attention response. In this connection it is relevant to recall that high-frequency stimulation of the medial cortical areas under consideration may also result in a widespread desynchronization or arousal effect of the electrocortical activity similar to that obtained on intralaminar stimulation (for references cf. Kaada,[11 pp. 279 and 295]). It has previously been suggested that this cortically induced effect on the electrocortical activity similarly is most likely mediated through the brain stem activating system.[11 p. 295]

Taken together, quite similar behavioral, somato-motor and electrocorticographic effects may be obtained on electrical stimulation of the intralaminar nuclei and of the medial cortical areas in question; this seems to indicate a close functional relationship.

A similar, but weaker, quieting influence on spontaneous movements has also been obtained from an area of the middle and posterior parts of the first temporal convolution of the monkey[9] and from the corresponding area of the cat.[7, 8] Quite recently Huertas, O'Doherty, and Forster[5] have observed a desynchronization or flattening of the EEG record (termed by them "suppression") which from their description appears to be identical with the effects obtained on intralaminar and medial cortical stimulation. Also, the change in the animal's behavior, when it is stimulated in the waking state,[5] bears some resemblance to that obtained in the present study. Finally, French, Hernández-Peón, and Livingston[4] have demonstrated connections from this temporal area to the brain stem activating system.

It appears not unlikely, therefore, that there exists a temporal area of functional significance similar to that of the frontal, limbic, and amygdaloid areas.

The present study possibly has some bearing on prefrontal leucotomy in mental diseases. According to the current concept, the beneficial effects of this operation are considered to be due to the interruption of fibers interconnecting the prefrontal cortex and the dorsomedial thalamic nucleus. Our experiments indicate a second prefrontal-thalamic system which undoubtedly is interfered with in most instances in the usual leucotomy, particularly

when the lower medial quadrant of the white matter is included. Also, in thalamectomies intending to destroy the dorsomedial nucleus it seems almost inevitable not to encroach upon the adjoining n. centralis medialis, n. paracentralis, and n. centralis lateralis. It remains for future research to decide whether interruption of this second prefrontal-thalamic system has anything to do with the effects obtained in leucotomized patients. It will prove a difficult task, however, to destroy selectively in human patients the central nuclei with their laminar shape and their relatively great extent.

SUMMARY

1. Stimulation of the medial prefrontal cortical region through implanted electrodes in unanesthetized freely moving cats results in a typical "attention" or "searching" response characterized by dilatation of the pupils, pricking of the ears, quick glancing or searching movements to the contralateral side associated with raising of the head and foretrunk.

2. Attempts have been made by combined stimulation-ablation techniques to determine which subcortical structures are necessary for the elicitation of this response.

3. The "searching" response was abolished by lesions which included the anterior basal part of the internal capsule on the same side, or when part of the intralaminar nuclei of the thalamus (notably n. centralis medialis, n. paracentralis, and n. centralis lateralis) were destroyed bilaterally. Destruction of part of the central nuclei reduced the "searching" reaction, but complete disappearance of the response required a bilateral and total destruction of the same nuclei.

4. The "searching" response still persisted after the following lesions: bilateral destruction of the cingulum bundle, the fornices, the dorsomedial nuclei or the centre median of thalamus, the habenulae and striae medullares thalami. Also without effect were fairly extensive lesions of the anterior group of the thalamic nuclei, the caudate nuclei, the hypothalamus, and the tegmentum mesencephali on both sides.

5. The nature of the response, and the possible bearing of the described second prefrontal-thalamic system on prefrontal leucotomy in mental diseases, are discussed.

REFERENCES

1. Adey, W. R. and Meyer, M.: An experimental study of hippocampal afferent pathways from prefrontal and cingulate areas in the monkey. J. Anat. (Lond.), 1952, *86*, 58-74.

2. Akert, K.: Experimentelles zum Thema Epilepsie. Schweiz. Arch. Neurol. Psychiat., 1952, *69*, 365-367.

3. Feindel, W. and Gloor, P.: Comparison of electrographic effects of stimulation of the amygdala and brain stem reticular formation in cats. EEG clin. Neurophysiol., 1954, *6*, 389-402.

4. French, J. D., Hernández-Peón, R., and Livingston, R. B.: Projections from cortex to cephalic brain stem (reticular formation) in monkey. J. Neurophysiol., 1955, *18*, 74-95.

5. Gloor, P.: Electrophysiological studies on the connections of the amygdaloid nucleus in the cat. Part I: The neuronal organization of the amygdaloid projection system. EEG clin. Neurophysiol., 1955, *7*, 223-242.

6. Hines, M.: Control of movements by the cerebral cortex in primates. Biol. Rev., 1943, *18*, 1-31.

7. Huertas, J. and Forster, F. M.: Temporal lobe seizures in the monkey. Neurology, 1955, *5*, 329-332.

8. Huertas, J., O'Doherty, D. S., and Forster, F. M.: Evidence of suppression from the temporal lobe in the monkey. Arch. Neurol. Psychiat. (Chicago), 1953, *70*, 393.

9. Jansen, J., Jr. and Andersen, P.: Cit. Kaada, B. R.: Temporal lobe seizures. EEG clin. Neurophysiol., 1953 [Suppl. 4], 235-246).

10. Jimenez-Castellanos, J.: Thalamus of the cat in Horsley-Clarke coordinates. J. comp. Neurol., 1949, *91*, 307-330.

11. Kaada, B. R.: Somato-motor, autonomic and electrocorticographic responses to electrical stimulation of "rhinencephalic" and other structures in primates, cat and dog. Acta physiol. scand., 1951, *24* (suppl. 83), 285 pp.

12. Kaada, B. R., Andersen, P., and Jansen, J., Jr.: Stimulation of the amygdaloid nuclear complex in unanesthetized cats. Neurology, 1954, *4*, 48-64.

13. Kaada, B. R., Jansen, J., Jr., and Andersen, P.: Stimulation of the hippocampus and medial cortical areas in unanesthetized cats. Neurology, 1953, *3*, 844-857.

14. Rose, J. E. and Woolsey, C. N.: Structure and relations of limbic cortex and anterior thalamic nuclei in rabbit and cat. J. comp. Neurol., 1948, *89*, 279-340.

15. Tower, S. S.: Extrapyramidal action from the cat's cerebral cortex: motor and inhibitory. Brain, 1936, *59*, 408-444.

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EFFECT ON TEMPORAL LOBE SYNDROME OF LESIONS ELSEWHERE IN THE CEREBRAL CORTEX OF MONKEYS†

The interrelationships of the temporal and frontal poles, parts of the so-called association areas of the cerebral cortex, are of interest for the understanding of many behavioral processes. These are the cortical areas which are suspected of integrating complex behavioral activities since their removal or absence produces changes in total performance which can be objectively measured in various ways in both man and lesser primates.[1] In these regions, more than any others of the cortex, comparison of function between man and monkey has been profitable. The lobotomy and lobectomy procedures, now relatively common therapeutic measures for man, are based entirely upon previous studies in the monkey and the chimpanzee.[1, 7, 11, 18]

That a functional interrelationship between the various association areas exists is to be expected from what is known of developmental and structural sequences. Thus, the frontal and temporal areas, with which this paper deals, each have an extensive lateral region which develops very late in the evolution of cortical dominance; the cat and dog, for example, have relatively little actual cortical tissue in these areas. Each region has also a mesial part which belongs to archicortex, yet is closely associated with its more recently developed neocortical region. Each is an "association" area, and as such is not primarily related to either receptor or motor function; direct stimulation in either man or monkey produces no perceptible physical change. Each unit has marked bilaterality of function such that unilateral ablation from one hemisphere has little effect, while bilateral ablation causes notable alterations in behavior. Each region, furthermore, has multiple neuronal connections with the other. The lateral tip of the frontal pole and the lateral surface of the temporal, which are neocortical, have direct fiber tract connections.[2, 6] The mesial surfaces, both older regions, are also interconnected because area 24, the mesial rostral cingulate gyrus, sends fibers to the mesial surface of the temporal pole.[19]

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Investigation of functional relationships between these two areas becomes of added interest because in contrast to the above evidence of structural and functional similarities, the well-known syndromes which result from bilateral ablation of the two regions seem, in many ways, completely opposite. Bilateral ablation of the frontal poles is followed by an increase in total activity such that the monkey becomes restless, hyperactive, and has an exaggerated startle response.[3] But, the monkey with bilateral temporal ablations becomes sedentary, quiet, passive, and without fear.[8] These syndromes are easily distinguished in a monkey colony and it is difficult to find similarities between their patterns. For these reasons, therefore, it was decided to observe the combined effects of ablations from the two areas in an effort to find behavioral relationships, if such occurred.

METHOD

Eighteen normal monkeys, *Macaca mulatta*, were used in this series. All were observed over a period of months prior to operation. Normal EEGs were run throughout this period and at intervals following the operations. These will be reported elsewhere.

The monkeys then had unilateral or bilateral surgical ablations of the various frontal and temporal areas. These were carried out according to a well-routinized sterile procedure.[7] By the second postoperative day the animals were well enough recovered to be observed for changes in performance. Their total behavior was then observed and noted for a period of many months during the development and maintenance of their chronic syndromes.

Three ablations were performed in this series. The frontal ablation consisted of the removal of all tissue rostral to areas 6 and 8 of Brodmann (Fig. 1). The ablated areas were, thus, areas 9-12 inclusive. Temporal ablations were made, cutting directly through from the lateral surface of the temporal lobe to the mesial, at the level of the most lateral portion of the central sulcus above the Sylvian fissure (Fig. 2). Care was taken to remove all tissue below the Sylvian fissure and to reach the mesial surface. Occasionally, but not frequently, the anterior tip of the temporal ventricle was opened. A third ablation was carried out when the syndrome of the cingulate gyrus was found to be significant. Figure 3 shows the extent of the lesion which removed all of area 24 in the rostral portion of the cingulate gyrus.

Second and third operations were made only when the animals had been observed to reach a steady state following the initial procedure, usually after a period of about six months.

DATA

In the course of this study the well-known syndromes characteristic of ablations from a single association area were reproduced. These will be described briefly.

Frontal poles. Bilateral ablation of areas 9-12, the frontal association areas, always produces a great increase in total activity. There is a perseverative quality to the

FIG. 1.

FIG. 2.

FIG. 3.

FIG. 1. Photograph of brain showing removal of all tissue rostral to areas 6 and 8 (Brodmann).

FIG. 2. Specimen illustrating bilateral temporal ablations.

FIG. 3. Bilateral removal of area 24 in rostral part of cingulate gyrus.

performance. The monkeys become less aggressive but are very watchful of all activity about them. They can usually be seen, high in the backs of their cages, jumping about, vocalizing, and making faces. They will, however, descend to snatch food rapidly and then return to their perseverative hyperactivity. In spite of increased total activity, their pattern of performance is much more stereotyped than that preceding operation. They circle constantly, usually in a well-beaten pathway across and about their cages. When they are left alone, unwatched, their activity diminishes but is still greater than in the preoperative stage. This syndrome is permanent for at least a two-year period.

Area 24. Bilateral ablation of the cingulate area, in contrast, produces a quiet, passive, and "soft" animal which has lost aggressive tendencies and consequently is unable to exist in a cage with a normal companion who easily acquires food and all other preferential cage dominance.[9, 10, 14] These animals sit fairly still under observation; there is no hyperactivity and no perseveration. There is always some return to more normal function, an increase in the variability of performance.

Temporal poles. When the temporal lobes are removed bilaterally and when the mesial, ancient portion is included in the removal, the monkeys become passive, hypomotile, and are said to have lost fear and developed curiosity.[12] These are the animals which nose and smell anything which they observe. They are apparently without the fear and animosity toward man which is normally shown by this species of monkey. For example, the net in which they are caught will always produce signs of rage and fear in the normal monkey and in those which have had the frontal tips or cingulate gyri ablated. But the bilateral temporal animal calmly regards this net with an unusual amount of interest, as he does any other object brought to his attention. He maintains discrimination, however, since he will nose and smell anything but will eat only the foods which he recognizes. There is always, in this laboratory, some return to normal behavior following the bilateral ablation.

In this primary temporal procedure two elements were considered and eliminated because neither apparently had any effect in the observations to be reported here. A hemianopia from injury to the optic tract might alter behavior and must therefore be considered. But, in the present series, only two animals had a demonstrable hemianopia following removal of a temporal pole. In each the symptom was transient, lasting about two weeks following operation. In neither could any difference in the temporal syndrome be detected when the final operation had been completed. There is no evidence from the observations of others that hemianopia plays a part in the temporal syndrome.[7]

A second possibility which arises from observations of the animals' behavior is that olfactory sense plays some part in the syndrome. The olfactory tracts, mesial in the temporal pole, may easily be damaged by the operation. For this reason the olfactory tracts on the mesial surface of the frontal lobes were cut at a primary operation in two monkeys. It is assumed that the animals became, thus, anosmic although no change in behavior followed the procedure. When temporal poles were removed subsequently,

the full-blown temporal pole syndrome developed including the nosing, smelling, and tasting of objects which is characteristic. Absence of the sense of smell, then, did not in itself produce any of the characteristics of the temporal syndrome nor did it alter the subsequent development of that syndrome.

Combined lesions. Combined ablations of these areas produced, of course, a combination of symptoms. The total picture and the quality of the behavioral interaction is of interest. All combinations of seriatim ablations were made, using the six areas above noted, that is, left and right frontal and temporal poles and anterior cingulate areas. The final effect was always the same and had no relation to either the sequence of ablations or to the time interval between these.

Removal of both temporal and both frontal poles always resulted in an animal having marked and permanent behavioral changes which were far more deviant from the normal than those produced by either ablation alone. These monkeys if left alone appeared quiet and apathetic; if aroused by our approaching the cage, or by a noise, they produced a perseverative pattern which had many of the characteristics of the frontal animal, marching up, down, and about the cages incessantly. Although not as hyperactive as the frontal animals and not as quick or violent in their movements, they retained a "purposeless" increase in total activity from the frontal syndrome. They retained also the absence of fear and the increase in "curiosity" of the temporal animal; in fact, in some animals, both these qualities became increased following the total combined lesion.

When cingulate gyrus removal was added to temporal ablation, a great increase in the "soft," depressed, and hypomotile behavior appeared. These animals were thought by those tending them to be ill, for they sat quietly in a back corner of the cage and moved very little unless rather strongly disturbed. They also retained the absence of fear and the increased curiosity. At times we thought these animals were unable to recognize well-known objects such as bits of food. This is a quality mentioned by Bucy and Kluver in monkeys with temporal pole ablations. Such confusion in relation to objects offered seemed always greater when the cingulate had been added to the ablated temporal regions.

Addition of the cingulate gyrus to the ablation of frontal poles produced almost no effect. If the cingulate gyrus was the first region ablated, removal of the frontal poles produced the hyperactive perseverative pattern which was indistinguishable from that of primary frontal pole ablation. When, however, the cingulate ablation was added to a primary frontal pole removal, there followed a moderate and temporary reduction in total activ-

ity, less restlessness, and less apparent speed of movement. Within a week or two, however, these latter animals could not be distinguished from those having only the primary frontal pole ablations. Similarly, there was no real difference between those animals having all six areas removed and those having only frontal and temporal poles, although addition of the cingulate gyrus ablation to that of the other always produced a temporary increase in the hypomotility and passive element of the behavioral pattern.

The effect of total removal of these association regions known to have functional and structural connections was always, thus, one of increasing existing patterns, the total picture being that of a confused and perseverative animal—far less alert, in less adjustment with his environment, and with a tendency to greatly reduced variety of performance.

Other evidence of functional interrelationships was also found. As has been stated above, unilateral removal of either a frontal or temporal pole has been known for many years to have no visible effect on behavior. However, unilateral removal of one frontal pole and the temporal pole of the same side always caused some temporary slowing and reduction of activity—a quiet, "soft" animal with minimal loss of fear and with some perseveration in performance. Here the change was transient and disappeared within a week or two following operation. The effects of bilateral ablation of orbital frontal surface were also observed and were found to be similar to those which result from total frontal pole ablation except that their effect was temporary and less marked.

DISCUSSION

The result of these extensive operations which have, finally, removed every association area of the cortex except that lying in the parietal lobe, has been the production of an animal drastically limited in the pattern of his motor performance and in his reactions to his environment. This is what was to be expected from previous knowledge but throws additional light on the total function of these areas in the normal state.

Firstly, no physical change of any sort was observed in these monkeys following any ablation. The observations were entirely on behavior and on cage performance, and no special measures of physiological function were carried out. But careful day to day observation suggested no field to which such observations could be directed. Only the specific behavioral symptoms of the syndrome of each ablation appeared. There was no change in gastrointestinal function as observed by intake and elimination; there was no marked change in urinary output; the autonomic system appeared unaltered as there was no pallor and no detectable change in vasomotor reactions; no

paresis nor obvious sensory deficit resulted. There were no clinical epileptic seizures.

The outstanding changes in behavior can be related to two qualities and, ultimately, to a single change. With successive ablations these animals showed an increasing reduction in the variety of pattern of their performance. Perseveration and stereotypy were marked. They appeared to have a markedly diminished appreciation of and reaction to their environment. All objects or data perceived from the outside world were treated in the same way: i.e., by the temporal animal, by picking up, nosing, or smelling anything; by the frontal animal, by excessive and "purposeless" movement. There did not seem to be, however, any ultimate loss of discrimination with regard to these immediate stimuli. Recognition of food objects was immediate in every instance. The loss of variety of response to environment became greatly exaggerated with the combined lesions such that the animals appeared barely able to carry out cage activity in such a way as to maintain adequate health and nourishment.

It is difficult to analyze the syndrome with respect to its psychological significance; detailed analysis of learning and behavior by means of training techniques should ultimately be carried out in such animals. But the one quality previously detected by Jacobsen[3] and then by Malmo,[9] that of impaired immediate memory following frontal pole ablation, can be related to these patterns of performance if immediate memory be considered as related to the meaning of environmental objects. There are at present no such data for the temporal lobe in the monkey, but in man, memory patterns have been shown to have some integration in the mesial temporal areas.[10]

It seems possible, then, from present evidence that the combined syndrome has for its basic patterning an impairment of memory, recall or association, and that the interconnections of the frontal and temporal association regions may normally serve for integration of this elaborate function. The hyperactivity of the frontal animal would then be a pattern resulting from removal of motor association which must be so integrated in the intact animal as to result in less violent and more appropriate behavior. The slow and "soft" quality of motor performance of the cingulate or temporal animal is less easy to interpret but a similar reduction in motor performance is reported in man as related to the cingulate area.[5] Bilateral ablations of the temporal poles in man are rare and no comparable observations have been reported for this region.

The relationship between archi- and neocortical areas adds further light as to the functional connections of frontal and temporal poles. The old, mesial portion of the temporal pole and the cingulate gyrus must be con-

sidered as one unit from all evidence now available. These structures are early developed and directly connected one with the other. Their seriatim ablation in these monkeys produced augmentation of what is known as the temporal lobe syndrome. They are probably, then, parts of a single, relatively simple, and undifferentiated system which has been early elaborated in cortical development. The fact that the cingulate area has been shown to be a strong suppressor area,[6] and that it is related directly and specifically to the reticular system of the brain stem, emphasizes the fact that this archicortical system must have a basic and generalized function within the forebrain. This, according to the behavior of the animals of the present series and to the description by others of monkeys having partial lesions of the system, may relate to total emotional behavior and to some form of memory or recognition of the meaning of the environment.

The part played by the neocortical structures in relation to these functions is less clear, possibly because it is less fundamental and intense and more truly of an associative, elaborative character. The syndrome of total ablation of both neocortical areas was always a more intense pattern of deviation from normal than the syndrome which resulted from the partial ablation when either the frontal or temporal lateral cortical surfaces were left intact. There was an effect on the frontal lobotomy syndrome from temporal lateral ablation, thus demonstrating functional interrelationship. Primary removal of temporal lateral poles alone, however, has never caused any change in pattern of performance. Damage to these regions in man may be followed by emotional lability and by psychomotor seizures. No such patterns have been observed in the monkeys' simple cage behavior. From our basic knowledge of the temporal pole one would expect its associative qualities to be related on the one hand to auditory and olfactory function, and on the other to the elaboration and complex organization of behavior in response to very highly integrated learned patterns derived from emotionally charged environmental situations.

CONCLUSIONS

In a series of eighteen *Macaca mulatta*, combined seriatim lesions of frontal association areas 9-12, temporal association areas and anterior cingulate regions, area 24, have been made. The resultant behavioral changes have been studied.

1. No simple motor, sensory, or autonomic change resulted from either partial or total ablation of all these regions.

2. Seriatim removal of these areas always produced a more and more profound deviation from the normal pattern of behavior. Two basic qualities

governed these changes: (a) an increasing limitation in the variability and adaptability of performance such that limited and perseverative activity resulted; and (b) a change in the relation to environmental objects which seemed to indicate a reduction in recognition of or reaction to the environment. This latter may have been the fundamental cause of the perseveration. It may have direct relationship to alterations in memory pattern which have been demonstrated by others in man and in the monkey.

3. These experiments illustrate the fact that the cingulate and the mesial portion of the temporal pole must be considered as one functional undifferentiated unit, and that these areas are directly related functionally to their more recently acquired frontal and temporal associative regions.

REFERENCES

1. Fulton, J. F.: *Frontal lobotomy and affective behavior.* New York, W. W. Norton & Company, Inc., 1951, 159 pp.
2. Fulton, J. F., Pribram, K. H., Stevenson, J. A. F., and Wall, P. D.: Interrelations between orbital gyrus, insula, temporal tip, and anterior cingulate. Trans. Amer. neurol. Ass., 1949, 175-179.
3. Jacobsen, C. F.: Functions of frontal association areas in primates. Arch. Neurol. Psychiat. (Chicago), 1935, *33*, 558-569.
4. Kennard, M. A.: Effect of bilateral ablation of cingulate area on behavior of cats. J. Neurophysiol., 1955, *18*, 159-169.
5. Kennard, M. A.: The cingulate gyrus in relation to consciousness. J. nerv. ment. Dis., 1955, *121*, 34-39.
6. Kennard, M. A. and McCulloch, W. S.: Functional organization of frontal poles of chimpanzees. Trans. Amer. neurol. Ass., 1942, 71-73.
7. Kennard, M. A., Spencer, S., and Fountain, G., Jr.: Hyperactivity in monkeys following lesions of the frontal lobes. J. Neurophysiol., 1941, *4*, 512-524.
8. Kluver, H. and Bucy, P. C.: An analysis of certain effects of bilateral temporal lobectomy in the Rhesus monkey with special reference to "psychic blindness." J. Physiol., 1938, *5*, 33-54.
9. Malmo, R. B.: Interference factors in delayed response in monkeys after removal of frontal lobes. J. Neurophysiol., 1942, *5*, 295-308.
10. Penfield, W.: Memory mechanisms. Arch. Neurol. Psychiat. (Chicago), 1952, *67*, 178-198.
11. Smith, W. K.: The functional significance of the rostral cingular cortex as revealed by its responses to electrical stimulation. J. Neurophysiol., 1945, *8*, 241-255.
12. Thomson, A. F. and Walker, A. E.: Behavioral alterations following lesions of the medial surface of the temporal lobe. Folia psychiat. (Amst.), 1950, *53*, 444-452.
13. Ward, A. A., Jr.: The cingulate gyrus: Area 24. J. Neurophysiol., 1948, *11*, 13-23.
14. Yakovlev, P. I., Hamlin, H., and Sweet, W. H.: Frontal lobotomy, neuroanatomical observations. J. Neuropath., 1950, *9*, 250-285.

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POSTCENTRAL AND PRECENTRAL CORTICAL LESIONS RESULTING IN CONTRALATERAL SKIN TEMPERATURE DISTURBANCES. THE PROBABLE NEUROPHYSIOLOGICAL ROUTES INVOLVED†‡

In a series of animals being studied for motor performance after parietal area ablations (earlier communications[2] with Dr. M. A. Kennard) skin temperature readings were taken from the extremities with the intention of studying these preparations further. Significant, sometimes wide, differences in skin temperature were obtained in these parietal preparations. It was decided, therefore, to explore by the method of extirpation the various regions of the cerebral cortex for their effects on skin temperature regulation.

MATERIAL AND METHOD

The subjects from which experimental data were obtained were 15 immature monkeys (13 *M. mulatta* and 2 mangabeys (*Cercocebus torquatus* Atys). These animals were studied for skin temperature differences over a course of from ten days to eight months. In 25 operations on these animals, various areas of the precentral and postcentral cortex were removed. The ablations were according to the known outline of Brodmann's areas. The extent of the various operations is described below with the experimental observations.

Temperature readings were obtained from symmetrical points on the soles of the feet by use of the automatically recording Micromax thermocouple instrument. The third lead was taken from the rectum. Environmental temperature was recorded periodically by the experimenter. During observations the animal was kept on its back in a holding box which permitted free movement of the lower extremities. Environmental humidity was found not to influence the data sufficiently to be given consideration. For eliciting vasomotor reflexes, the environmental temperature was suddenly altered by transporting the animal into a refrigerated room (temperature 39° F.). After varying times of such exposure the animal was returned to a warm environment. Skin temperature was continuously recorded. In wintertime similar effects could be produced by exposing animals to outdoor temperatures.

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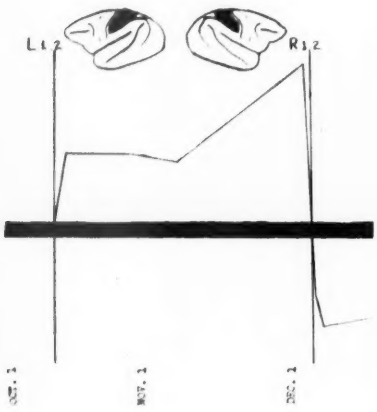
OBSERVATIONS

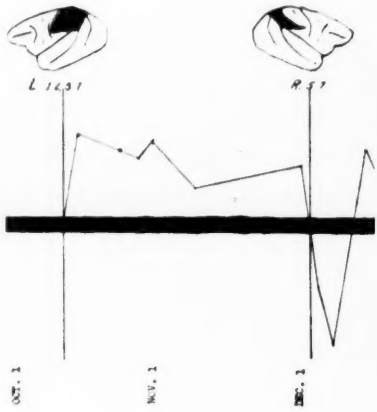
A. ILLUSTRATIVE TOTAL EXPERIMENTS

Experiment 1. Ablation of left areas 1-2 followed by right areas 1-2. After left ablation, the right extremities showed markedly lowered temperature; after right ablation, temperature of left extremities became lower than right.

First operation: left postcentral gyrus (Oct. 13, 1938). P. C. VII, Tattoo 1068. Areas 1 and 2 were removed, care being taken not to injure any portion of area 4.



GRAPH 1.



GRAPH 2.

GRAPH 1. Postcentral VII, No. 1068. Left postcentral gyrus ablation followed by right. Heavy baseline gives a calibration of 1° F. It everywhere represents the temperature of the right lower extremity with relation to the left (thin black line). Length of black line represents period of study. Solid black areas on cortical maps represent areas ablated.

GRAPH 2. Postcentral VI, No. 1034. Left parietal area ablation followed by right posterior parietal area. Note transient effect of second smaller ablation.

There was rapid recovery from the operation. Hand preference was for the left hand, but rhythmic movements of progression were performed well by both sets of extremities. During skin temperature readings there was about the same amount of motor activity in each extremity. The right lower extremity showed persistently a lower skin temperature than the left. On one occasion an 11° F. difference was obtained (see graph 1).

Second operation: right postcentral gyrus (Dec. 5, 1938). Areas 1 and 2 were removed as in first operation. Recovery was rapid with very little postural defect. After this operation the left extremity now had a lower temperature than the right, the largest difference recorded being 6.5° F.

The data on this animal show definitely that ablation of a relatively small area of the postcentral cortex can produce a profound effect on the skin temperature of the opposite extremities. It also demonstrates that the acute effect after an ablation is greater than that exerted long after an ablation. The bilateral lesions being anatomically equivalent, one would otherwise expect no difference or at best a slight difference in skin temperature after the second operation.

Experiment 2. Ablation of left areas 1-2-5-7 followed by right areas 5-7. After first operation right extremities were constantly lower in temperature than left. After second operation, transient lowering of skin temperature of left extremities was followed by resumption of previous status.

First operation: left parietal lobe (Oct. 12, 1938). P.C. VI, Tattoo 1034. Ablation of left areas 1,2,5,7, care being taken not to approach the region of area 4. Static postural defect postoperatively; practically no motor defect during automatic progression. Right extremity had a persistently lowered skin temperature as compared to the left, the largest recorded disparity being 6° F.

Second operation: ablation right areas 5 and 7 (Dec. 2, 1938). In this operation the posterior parietal region was removed. No injury could possibly be sustained by the motor region. The animal showed transient preference for the right extremities and then resumed preference for the left limbs. For nine days postoperatively the left extremities had a lower skin temperature than the right (max. difference, 8° F.). Thereafter, the right again showed a lower temperature as compared to the left (see graph 2).

This experiment substantiates the data of Experiment 1 and tends to indicate one other factor. If the bilateral parietal lesions are unequal in extent, in the chronic state the extremities opposite the larger lesions will have the lower temperature. It seems significant that a region of the cortex as posteriorly placed as areas 5 and 7 can exert a considerable though transient effect upon limb temperature.

Experiment 3. Ablation of left areas 6 and 8 followed by right areas 1, 2, 5, 7. After first operation right extremities were slightly lower in temperature than left but not constantly so. After second operation left extremities were considerably lower in temperature than right.

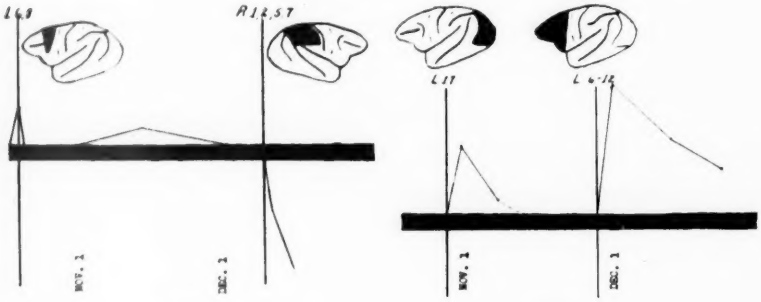
First operation: left areas 6 and 8 (Oct. 19, 1938). P.C. VIII, Tattoo 1073. Ablation of left areas 6 and 8. Transient deviation of eyes to side of lesion. Definite right hemiparesis which gradually became less marked. On halt the tests the right extremity had a lower temperature than the left; largest difference, 3° F. On the other readings the temperature was equal in both extremities (graph 3).

Second operation: right parietal area (Dec. 7, 1938). Ablation of right areas 1,2,5,7. Transient faulty use of left extremities even in automatic progression. Left lower extremity showed a markedly lowered skin temperature as compared to the right. The maximum difference recorded was 8° F.

This experiment shows that a parietal ablation may have a greater effect upon the contralateral skin temperature than an ablation of area 6. Of course the ablation in the parietal area was larger than that in the premotor area, and this factor of amount of cortex removed may be the significant thing rather than the specific location of that area (graph 3).

Experiment 4. Ablation of left occipital lobe followed by left areas 6 through 12. There was a transient lowering of skin temperature of right extremities with potentiation of the effect after second operation.

First operation: left occipital lobe (Oct. 28, 1938), P.C. IX, Tattoo 1052. Extirpation of left occipital lobe with some sparing of the medial aspect of the occipital region.



GRAPH 3. GRAPH 4.

GRAPH 3. Postcentral VIII, No. 1073. Left premotor area ablation followed by right parietal area. Note that the larger parietal ablation produces greater temperature differences than the smaller premotor ablation.

GRAPH 4. Postcentral IX, No. 1052. Left occipital lobectomy followed by removal of ipsilateral frontal lobe (see text).

Right incomplete hemianopsia which disappeared. Transient lowering of skin temperature of the right lower extremity; maximum difference, 5° F. (see graph 4).

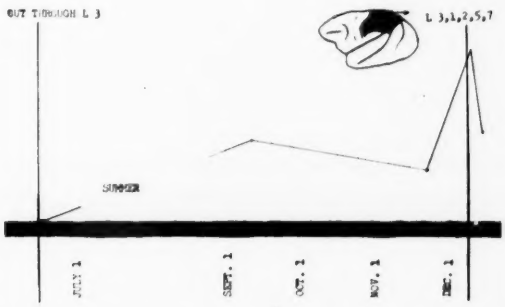
Second operation: left areas 6 through 12 (Nov. 28, 1938). Extirpation of left frontal lobe anterior to area 4 carried out. Rhythmic progression carried out normally. Marked difference now between skin temperature of extremities, right lower than left; maximum difference 9° F. (graph 4).

This experiment shows that an area as remote from the frontal region as the occipital lobe exerts an effect upon skin temperature. An additional ipsilateral extirpation increases the depression of skin temperature in the contralateral extremity.

Experiment 5. Left-sided section of transcortical U-fibers between pre- and postcentral gyri was followed by ablation of left parietal region. First

operation was followed by lowering of skin temperature of right extremities. Second operation increased difference of skin temperatures.

First operation: section of U-fibers between pre- and postcentral gyri (June 14, 1938), P.C. IV, Tattoo 1032. Central sulcus opened to its depth. All white matter under the depths of sulcus bisected for 8 mm. Moderate right hemiparesis which after two months was almost not demonstrable. Constant lowering of skin temperature of right lower extremity as compared to left over a period just short of six months; maximum difference, 6° F. (see graph 5).



GRAPH 5. Postcentral IV, No. 1032. Cut through posterior lip of central sulcus; later parietal area ablation. Note prolonged effect on skin temperature differences by merely cutting of U fibers.

Second operation: removal of left parietal region (Dec. 9, 1938). Extirpation of left areas 3,1,2,5,7 behind the previous transcortical cut. Disinclination to use right extremities volitionally but automatic movements were well carried out. Increase in the disparity of skin temperatures already present between right and left extremities; maximum difference 12° F. (graph 5).

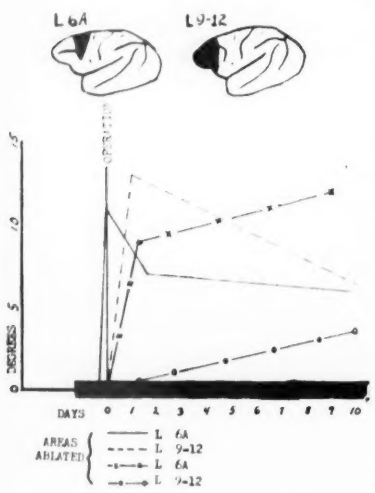
Here again the parietal ablation was performed without injury to the motor cortex as the previous operations had definitely separated the two regions of the cortex. Yet a maximal difference in temperature between the two extremities was obtained. The constancy of the effect upon skin temperature over a period of six months is noteworthy.

Experiment 6. Ablation of left area 6A (2 animals) and left areas 9 through 12 (2 animals) with subsequent study of skin temperature differences in the extremities for ten days. Both types of ablation lowered temperature in contralateral extremity equivalently.

Ablation of left area 6A (2 animals). (T.C. Nos. 7, 4, 6, 12). Extirpation of left area 6A, hand and foot area. Recovery from operation with little paresis. Right lower extremity persistently lower in skin temperature than left for the period of study (10 days); the maximum difference was 12° F. (see graph 6).

Removal of prefrontal areas, (9-12), (2 animals). The entire region of the frontal lobe anterior to area 6 was removed. Little if any paralysis was noted. Right lower extremity recorded as lower in skin temperature than left; the maximum difference recorded was 13° F.

These experiments show that areas as inert from a motor or sensory standpoint as the frontal poles still exert an effect upon skin temperature regulation of the opposite extremities. These regions of the cortex may be endowed with vasomotor neurones.



GRAPH 6. Skin temperature differences in extremities noted after premotor and frontal pole ablations.

Experiment 7. Ablations seriatim of left areas 3,1,2; right areas 3,1,2; left areas 5,7, and portions of 18; and right areas 5 and 7. Each extirpation of cortex had the effect of at least lowering the skin temperature of the contralateral extremity transiently. Whenever lesions were unequal in extent, side opposite larger lesion had lower skin temperature.

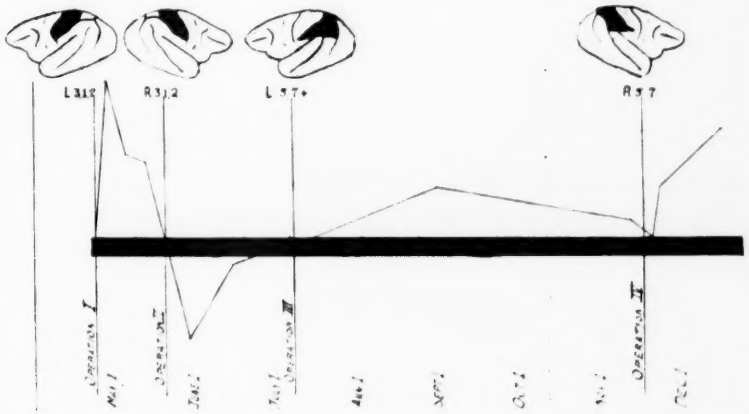
First operation: left postcentral gyrus (April 22, 1938). P.C. I, Tattoo 972. Extirpation of left areas 3, 1, 2. Practically no motor defect in rhythmic progression. Skin temperature of right lower extremity persistently lower than left; maximum difference 10° F. (see graph 7).

Second operation: right postcentral gyrus (May 18, 1938). Extirpation of right areas 3,1,2. Little motor effect on rhythmic progression. Skilled acts poorly performed. Skin temperature of left lower extremity transiently lower than right with tendency to equal that of right extremity in the chronic stage; maximum difference, 5.5° F.

Third operation: extirpation of left posterior parietal region (July 7, 1938). Extirpation of areas 5, 7, and parts of 18 and 19 behind the previous ablation. Automatic progression still without major difficulty. Skin temperature of right lower extremity persistently lower over many months than left, but maximum difference is less marked (3.5° F.).

Fourth operation: extirpation of right posterior parietal region (Nov. 16, 1938). Extirpation of right areas 5 and 7 behind previous ablation. Insecurity in use of all extremities postoperatively. Skin temperatures transiently equal in both lower extremities; then the right became lower than the left.

In a series of seriatim ablations, the effects registered on skin temperature followed expectations in each case. After equivalent bilateral extirpations, the temperatures became approximately equal. After completion of all four operations, the amount of cortex ablated on the left side was found to be greater than on the right. As a result the right extremities became lower in temperature than the left.



GRAPH 7. Seriatim ablations of each postcentral gyrus followed by each posterior parietal area (see text).

Experiment 8. Simple craniotomy flap. Exposure of premotor, motor, and parietal cortex for 15 minutes. Usual closure. Skin temperature equal bilaterally following procedure.

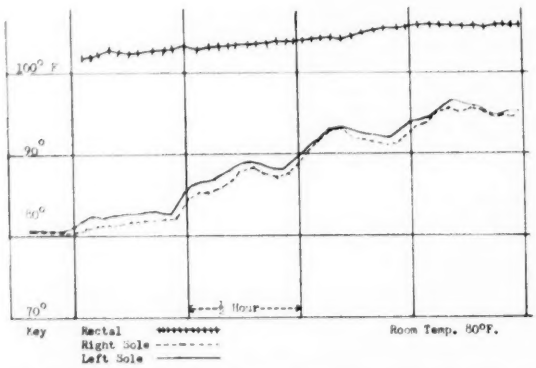
Operation: left fronto-parietal craniotomy flap (Nov. 14, 1938). P.C. XI, Tattoo 1113. Usual procedure in laying down craniotomy flap. Premotor, motor, and parietal cortex exposed for 15 minutes. Dura sutured and flap replaced as usual. No difference in skin temperature between extremities postoperatively.

This experiment is a control to show that it is not operative trauma to the premotor cortex or any other cortex which yields skin temperature differences after cortical ablations other than area 6.

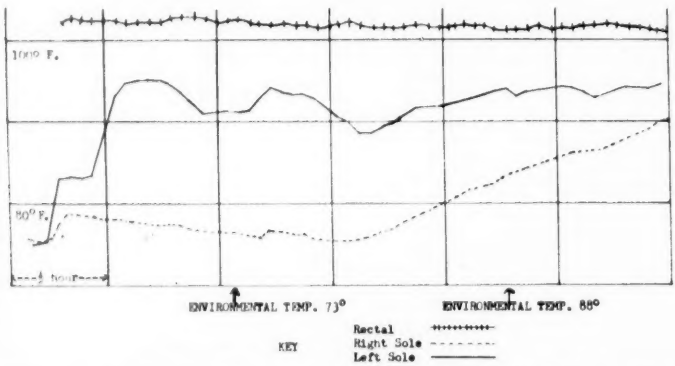
B. OBSERVATIONS DERIVED FROM THE EXPERIMENTAL RECORD

Certain temperature records were illustrative of points which require mention and interpretation. Record 1 shows that apparently waves of vasodilatation are sent forth periodically from a temperature regulatory center

in adaptation to the organism's heat dissipatory needs. (The needs may be stated to be due to a steadily rising body temperature.) These vasodilatory sendings may be directly centrifugal from the so-called thermostat in the hypothalamus to the spinal sympathetic centers, or may be mediated via the cortex for lateralizing effect.

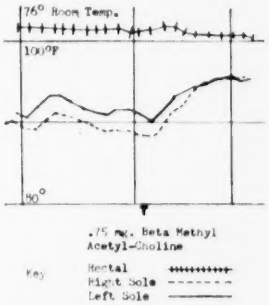


RECORD 1. Temperature in both extremities approximately equivalent. Environmental temperature constant at 80°. Both extremities simultaneously experience waves of increase in skin temperature. Periodicity between 15 and 25 minutes. Rectal temperature steadily rising.



RECORD 2. Temperature recording in animal probably with edema of entire left hemisphere. This followed retraction on the occipital lobe for mid-line exposure. Animal transiently hemiparetic, dull, and apparently suffering headache. Gradually increasing environmental temperature. Practically no effect on right extremity for 1½ hours. Immediate maximal vasodilatory effect on normal left extremity with additional waves as extremity tended to cool. Rectal temperature remained constant. Slow warming of right extremity without waves. Maximum difference in skin temperature 17° F. (Anterior cerebellar series)

In order to maintain body temperature constant the thermostat sends out nervous waves intended to produce vasodilatation in both sets of extremities. *Because these waves are probably mediated through the hemispheres,* the animal of record *2* showed an effect of vasodilatation on the normal left extremities only. The left hemisphere in this case was almost totally functionless. Thus, the vessels in the left extremities had to be kept persistently dilated for maintenance of normal body temperature. The normal right cerebral hemisphere could transmit the impulses from the thermostat to the left extremities whereas the left hemisphere could not. It would seem therefore that the hypothalamic thermostatic center must send its centrifugal fibers upward to the cerebral cortex for lateralization before they reach the spinal autonomic centers.



RECORD 3. Section of record showing effect of mecholyl upon a pre-existing difference in skin temperature. Temperature of both extremities elevated and now the left equals the right. Note lowering of body temperature as skin vessels dilate maximally throughout the body.

Record 3 shows that while the temperature of the two extremities is maintained at a steady difference due to unequal cortical supply, a peripherally acting vasodilator can render the skin temperatures equivalent.

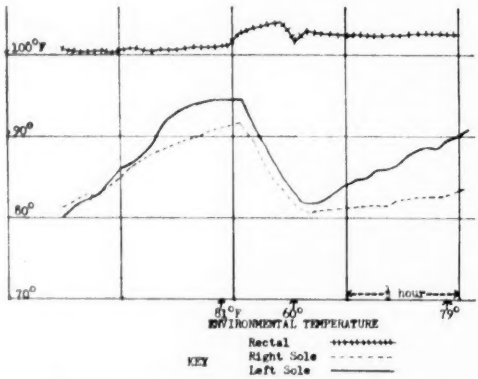
Record 4 illustrates a vasodilatory reflex which becomes defective on one side when there is an unequal cortical sympathetic supply from the hemispheres. Kennard[7] has described this finding in a previous paper.

DISCUSSION

For a number of sound reasons physiologists have postulated a thermostatic center in the central nervous system. The probable location of this center in the hypothalamus has been deduced from copious experimental data.[1-5] For maintenance of heat dissipation, this thermostatic center periodically sends centrifugal nerve impulses to the spinal autonomic centers which result in peripheral vasodilatation. The waves of vasodilatation noted in the experimental record probably represent these periodic discharges.

Ablation of almost any region of the cerebral cortex seems to block these vasodilatory messages to the extremities opposite the side of the lesion. In the case of a totally functionless cerebral hemisphere (record *2*) the waves of vasodilatation are not seen in the paralytic extremity while the tempera-

ture of the normal extremity is maintained at almost a maximal level. Lesser disturbances in function in the cerebral cortex (record 4) result in depression of the skin temperatures of the opposite extremities. From these extremities waves of vasodilatation may be recorded but they are usually more shallow and less frequent in occurrence than in the normal extremity. That vasodilatation in the affected extremities is not complete is deduced from record 3. Here a peripherally acting vasodilator renders the skin temperature of opposite extremities equal immediately. It seems logical, therefore, to draw the conclusion that vasodilatory impulses, if they arise



RECORD 4. Record taken following ablation in left hemisphere. Temperatures start out equivalently until environmental temperature is elevated. Left extremity takes on a higher temperature than right. Environmental temperature is sharply lowered; then elevated. There is a reinforcement of the difference.

from the thermostatic center, have synapse with cortical sympathetic neurones whence the impulses are invested with a specific lateralization.

The records obtained in this series and in Kennard's earlier work indicate that vasoconstriction is equivalent in symmetrical extremities whatever the difference in skin temperature might have been previously. Vasoconstriction comes on rapidly, and a maximal state is quickly attained. The thermostatic center can probably send forth impulses for vasoconstriction. However, the experimental data herein presented indicate that the route of this impulse is certainly not via the cerebral cortex. Indeed, it would seem that the response of vasoconstriction to lowering the environmental temperature is merely over a spinal reflex arc. Cortical ablation would thus exert very little influence over the vasoconstrictive reflex.

Another theory of the mechanism of vasomotor regulation in the extremities is possible on the basis of the experimental data. Vasodilatation may occur as the result of a complex reflex arc, arising within the extremities and making use of cortical neurones in the opposite cerebral hemisphere. This latter point is postulated because cortical ablations disturb the reflex. In this reflex arc, the thermostatic center may or may not be a way station. Elevation in environmental temperature with relation to the limbs would be the adequate stimulus for the reflex. The waves of vasodilatation indicate that there is a periodic initiation of the reflex. This suggests that after one reflex discharge a certain increment of environmental temperature must accumulate before the reflex is again precipitated. Such a vasodilatory system would be in tonic antagonism with the vasoconstrictive reflex system. Impaired effectiveness of the former (cortical ablation) would result in peripheral vasoconstriction and a colder extremity. This theory is amenable to further experimental elucidation.

SUMMARY

The results of the experiments performed may be summarized in the following manner:

1. Ablation of area 1, areas 2 and 5, areas 7, 17, and 6, or areas 9 through 12 yields an effect upon the skin temperature of the contralateral extremity which in this series has always been in the direction of lowering as compared to the normal extremity.

2. The effect persists for months.

3. If equivalent lesions in each hemisphere are made seriatim, the extremity opposite the latest ablation will have the lower temperature.

4. If unequal lesions in each hemisphere are made seriatim, there will be the transient effect of the latest operation followed by resumption of a state where the lower skin temperature is on the side opposite the larger ablation.

5. Parietal ablations seem to be as significant as premotor ablations for this effect on skin temperature.

Because changes in skin temperature have been found with paralysis of extremities, objection has been voiced that the low skin temperature is merely a reflection of decreased blood flow to that extremity. This objection seems well answered by the experimental data herein presented. Vast skin temperature differences appear after ablations in the frontal and occipital poles. These areas are certainly inert from the standpoint of producing motor paralysis. Ablations in postcentral cortical areas result in difficulties with fine acral movements; no true paralysis occurs, however. In this

series, lesions in the postcentral region always yielded significant depressions of skin temperature in the contralateral extremities.

The evidence of the experimental data seems to point to the conclusion that the cerebral cortex is diffusely supplied with autonomic neurones. Such an assumption does not provoke accepted theory too far. In the course of evolution of the species, acral functions of extremities have become largely encephalized. Acral autonomic control may have been simultaneously corticalized.

The fact that ablations anywhere in the cortex affect skin temperatures indicates that in the process of encephalization the autonomic nervous system did not confine itself within definite bounds. This nervous system elsewhere does not lend itself to anatomic pigeon-holing. It must follow this same tendency in its distribution throughout the cerebral cortex. Perhaps the major concentration of autonomic neurones is in the premotor, motor, and parietal cortex, but ramifications extend to the frontal and occipital poles. The data from this series of experiments predicate the following postulate: In a given animal, the effect of a cortical ablation upon skin temperature in the opposite extremity is dependent upon the amount of cortical tissue removed.

REFERENCES

1. Hemingway, A., Rasmussen, T., Wikoff, H., and Rasmussen, A. T.: Effects of heating hypothalamus of dogs by diathermy. J. Neurophysiol., 1940, *3*, 329.
2. Kennard, Margaret A. and Kessler, M. M.: Studies of motor performance after parietal ablations in monkeys. J. Neurophysiol., 1940, *3*, 248-257.
3. Kennard, Margaret A.: Vasomotor disturbances resulting from cortical lesions. Arch. Neurol. Psychiat. (Chicago), 1935, *33*, 537-545.
4. Magoun, H. W., Harrison, F., Brobeck, J. R., and Ranson, S. W.: Activation of heat loss mechanisms by local heating of the brain. J. Neurophysiol., 1938, *1*, 101.
5. Strom, G.: Vasomotor responses to thermal and electrical stimulation of frontal lobe and hypothalamus. Acta physiol. scand., 1950, suppl. 70, *20*, 83.

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A METHOD FOR THE ESTIMATION OF REGIONAL CEREBRAL BLOOD FLOW§

Over the past years the nitrous oxide absorption method proposed by Kety and Schmidt[12] has achieved wide application for the estimation of the blood flow through the cerebral tissue as a whole. However, histological evidence indicates a great variability in the relative vascularity of the several portions of the brain. Thus, for the most part, the white matter is relatively poorly supplied with blood vessels, while the gray matter, on the other hand, is very vascular. Some indication of the variable distribution of blood flow through the brain has been obtained by use of the so-called Gibbs needle Stromuhr.[5, 13] Another approach to the measurement of local blood flow is the observation of the pial blood vessels through windows[8] or through the somewhat more satisfactory lucite calvarium.[17] At best, these methods estimate the *caliber* of the pial blood vessels, but actually give little information about the blood flow through these small blood vessels. Recently Kety[9] has reported on a highly sensitive method for simultaneous measurement of blood flow through all regions of the brain. This method involves equilibration of cerebral tissue with a radioactive gas brought to the brain by the normal circulation; from the relative concentration of gas in the several areas of the brain, estimates of regional blood flow may be made. Since the animal must be sacrificed at the moment of the estimation of blood flow, this method cannot be used to follow progressive changes.

The Kety isotope tissue clearance technique[7] has been applied to a large variety of tissues.[1, 2, 14, 16] Attempts to extend this method to cerebral circulation were made by Kety[11] who measured the rate of removal of Na^{24}, and of an isotopically labeled gas, from various injection sites in the brain. The data did not satisfy him, however, and he has abandoned this approach. Boatman[1] measured the clearance of Na^{24}, I^{131}, and $I^{132}O_3$ from areas in the

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brains of dogs and rats, but in these studies there was no precise localization of the injection site, and the disappearance rates were followed for periods of only 10 to 15 minutes. We decided to extend and elaborate the tissue isotope clearance technique for the determination of regional blood flow in the brain by applying the Horsley-Clarke stereotaxic instrument for the more precise localization of the injection, by extending the period of measurement to 80 minutes, and by applying certain indicated corrections to the data. The results of our studies indicate that with proper precautions this method may be used to estimate *changes* in blood flow through the brain.

METHODS

In these experiments a small, measured volume of saline containing an appropriate radioisotope was injected into specific, localized areas of the brains of animals using a Horsley-Clarke stereotaxic instrument as described below. The amount of isotope remaining at the injection site was determined by use of Geiger counting tubes and auxiliary equipment.

All studies were carried out on mature cats of both sexes, weighing between five and fourteen pounds; these animals were all in good health but were not otherwise selected. The animals were for the duration of the experiment maintained in the surgical plane of anesthesia with Nembutal (pentobarbitol sodium); 60 milligrams per five pounds of body weight were injected intraperitoneally, with a subcutaneous sustaining dose equivalent to one-half the initial amount.

Surgery consisted of two parts. In the first, a cephalad-directed cannula was inserted in one carotid artery to provide maximal concentrations of the infused material in the brain with minimal concentrations elsewhere. Blood pressures were recorded from this same cannula. Ligation of a single carotid artery imposes no serious disability upon the cerebral circulation of the cat.[16]

In the second phase, the skull was exposed and carefully trephined over the proposed site of injection as determined by means of the stereotaxic instrument.* The injection was made with a 1 ml. tuberculin syringe clamped in the electrode holder. A 26-gauge 1½-inch needle proved long enough to reach any part of the cat's brain. After each injection the needle was withdrawn, the surface area sponged to remove accidental isotope contamination, and the trephined hole was filled with bone wax.

The amount of the radioactive material remaining at the site of injection was followed by means of a Geiger-Muller tube placed about one inch above the skull. A layer of aluminum foil was placed over the window in order to minimize the danger of contamination.

To provide an approximation of the progressively increasing background count in the area of the injection due to recirculation of the isotope,[2] a second G-M tube was placed against the skin of the animal over the femoral region. Each of the G-M tubes

* Lab-Tronics Model No. 4.

was connected to a scaler unit; these in turn were connected to chronograph pens, thus providing a continuous record of the counting rates.

The isotope used in all cases was I^{131} or Na^{22}; both of these ions have been shown to be cleared in an identical fashion from the various tissues.[1, 8, 18] In the conditions of these experiments, approximately 50 microcuries provided a counting rate which was below the level that requires application of a coincidence correction (about 15,000 counts/min. with the equipment being utilized) and yet was high enough to maintain a level above 1,000 counts/min. (a level at which the plotted points began to scatter widely).

The rôle played by the volume injected is as yet unknown, but indications are that it may be an important one.[10] In the present studies this volume never exceeded 0.5 ml., the average volume being 0.25 ml.

TABLE 1. ISOTOPE CLEARANCE FROM THE INTERNAL CAPSULE

Isotope	*No. animals*	*No. exps.*	*K* (%/min.)	$t^{1}/_{2}$ (min.)	*Volume injected* ml.
I^{131}	27	64	1.14 .48	73.4 .32	0.30 .02
Na^{22}	8	8	1.06 .26	70.0 .20	0.13 .03

Dissolved agents were infused intra-arterially at a constant rate of 1 ml./min. by means of a simple mercury-driven syringe system. Gases were administrated by tracheal intubation, using a Tygon airway fitted with an inflated cuff to prevent leakage. The respiratory system was designed with minimum dead air space and provided with a spirometer for concurrent measurements of minute volume.

Electroencephalograms were made of a number of the animals during infusion. The recorded potentials, obtained from electrodes placed over the frontal and the lateral occipital areas of the skull, indicated that each agent manifested a definite effect upon the over-all electrical activity of the brain.

RESULTS

A series of 64 injections of radioactive iodine in the form of iodide was made directly into the internal capsule of the brains of 27 cats. In each case the semi-logarithmic plot of the disappearance curve showed several deviations from a purely exponential character. There was a rapid decrease in the amount of iodine remaining at the injection site during the first 15 to 20 minutes, followed by a somewhat slower and, for the most part, relatively linear disappearance over the ensuing 60 to 80 minutes. The slope of this line can be expressed in terms of per cent per minute removal. The data from all the experiments are combined in Table 1. The mean value for all determinations was 1.14% per minute (mean half time = 73.4 min.). Since the rate of removal of I^{131} from muscles is approximately 5% per minute,[19]

while blood flow through the brain as a whole is known to be greater than the blood flow through muscle, this discrepancy clearly limits the usefulness of clearance as an absolute measure of cerebral blood flow. This low disappearance rate might be explained if local binding of the isotope occurred by interaction of the iodide with some component of the brain. This possibility was ruled out in a small series of experiments using Na^{22}, which gave disappearance rates on the whole comparable with those obtained with I^{131}. Since it is unlikely that Na ion reacts with any component of brain tissue, "binding" cannot explain the low disappearance rate.

TABLE 2. EFFECT OF DRUGS ON I^{131} CLEARANCE FROM INTERNAL CAPSULE

Drug	*Dose (γkg./min.)*	*No. animals*	*No. exps.*	K_1 *before drug (%/min.)*	K_1 *after drug (%/min.)*	K_1/K_1	*Vol. isotope inj. ml.*	*BP after BP before*
Histamine	1.33 (0.5-2.5)*	14	19	1.21 .16	0.85 0.12	.72 ±07	.26 .03	.97 .02‡
Hydergine	.27 (0.025-.50)*	7	7	1.10 .11	1.98 .99	1.83 .23	.31 .07	1.11 .021‡

* Range of dosage.
‡ Determined on 8 cases.
‡ Determined on 3 cases.

The fact that in most cases a uniform, constant disappearance rate could be obtained after the 15th minute suggested the possibility that each animal might serve as his own control. To show that simple manipulation of the animal would not alter the measured disappearance rate, in a small series of animals the disappearance rate was determined before and during the intracarotid infusion of 0.9% sodium chloride. Figure 1 is an example of the results in one of these saline infusion experiments. There was no detectable change in the rate of disappearance with the onset of the saline infusion. It thus becomes possible to compare the disappearance rate during the period of infusion with the control or pre-infusion rate to measure the effect of any infusable agent on the clearance from any accessible region in the brain.

In a small series of 19 experiments, histamine* in concentrations of 0.25 to 2.5 micrograms per minute per kilogram of animal was infused into the carotid artery. In most of these cases there was a diminished clearance of iodine from the internal capsule. Blood pressures, as measured by the con-

* Histamine diphosphate, Abbott.

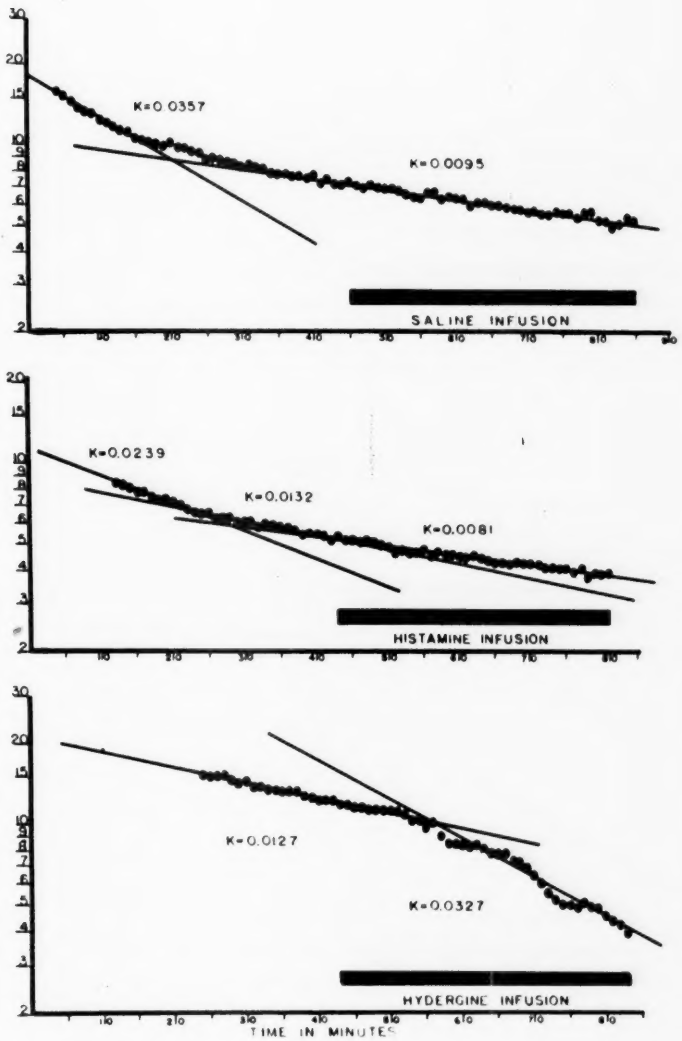

FIG. 1. Clearance of I^{131} from the internal capsule of the brain of the cat. Ordinates: Counts in thousands per minute at injection site, corrected for background. Abscissa: Time in minutes after injection of isotope.

ventional mercury manometer technique, are included along with the clearance values in Table 2. If the diminished clearance reflects a diminished blood flow, then these data suggest that histamine is in fact a constrictor in the blood vessels in the area of the internal capsule.

In another series of experiments, Hydergine®* was infused in exactly the same way as histamine was used. The dosage varied from 0.025 to 0.50 micrograms per kilogram per minute. The data obtained in these experiments are likewise included in Table 2. The increase in clearance observed in most of the Hydergine infusions is consistent with the information which we have concerning the effects of this agent on blood flow through the brain as a whole.

Characteristic electroencephalographic changes could be correlated with the infusion of either histamine or Hydergine. Histamine infusion consistently increased the sleep pattern in the record, while Hydergine infusion had the opposite effect. Alternate infusion of the two drugs resulted in corresponding alteration in the EEG tracings. The electrical activity changes could not be localized, however, but were manifested as an over-all phenomenon. The direction of the EEG changes suggests at least a parallel to the effects of the drugs on tissue clearance and the EEG records are thus taken as evidence to support the argument that blood flow changes are responsible for the changes in clearance.

DISCUSSION

The data presented suggest that Kety's tissue clearance technique may be extended to provide a clearer understanding of the regional cerebral circulation. In the special case of the brain, clearance of locally injected materials may not be entirely via the cerebral circulation. Other factors, such as the movement of the cerebrospinal fluid, must be taken into consideration; however, all available evidence would indicate that only blood flow could be altered with sufficient rapidity to account for the changes in clearance noted. Thus the circulatory system is probably the primary pathway for the removal of the isotope from the site of injection.

The discrepancy between the relative blood flow rates in muscle and brain compared to the clearance rates in these two tissues requires comment. Clearance will be determined to a marked degree by the relationship between the injected material and the capillaries and small blood vessels in the injected tissue. Kety originally assumed that the injected material was distributed in such a way as to cause minimal changes in local vascular

* Hydergine® is a mixture of hydrogenated ergot alkaloids containing the methanesulfonates of dihydroergocornine, dihydroergocristine and dihydroergocryptine.

arrangements. It may be that in the brain, a tissue with a high lipid content, the injected aqueous material becomes pocketed in such a way that clearance is delayed. Kety[10] suggests that the *shape* taken by such a bleb of injected tracer may significantly alter the rapidity of isotope removal: thus, an ameboid deposit, because of its greater surface, would be more rapidly removed than would be comparable spherical bleb. Still another explanation for the relatively low clearance rates would be the binding of the isotope at the injection site. That this explanation is not likely is indicated by the similarity of results of the studies with cations, Na^{22}, and anions, I^{131}.

It is difficult to relate our results with histamine to the earlier reports in the literature. Some previous studies have indicated that histamine dilates cerebral vessels[9, 19]; others showed that total cerebral blood flow might be increased, decreased, or unaltered after administration of this compound. However, in view of the profound effects on the blood pressure which occasionally occurred in the later experiments, the actual changes in cerebral vascular resistance are not clear. The present studies indicate that histamine causes diminished perfusion of the internal capsule; since the simultaneously determined blood pressures were only moderately depressed, we would believe that these data suggest vasoconstriction, rather than dilation as previously reported.

The electroencephalographic investigations showed that histamine produced a deepening of narcosis. This was evidenced by the accentuation of the sleep pattern recorded by the EEG. As the concentration of histamine was increased, the EEG manifestations of narcosis also increased. These results suggest that histamine potentiates the anesthetic. This might be explained on the basis that histamine is a vasoconstrictor. It is interesting to note that the altered electrical activity was obtained from all portions of the brain studied and was not limited to a specific focus.

The results obtained with Hydergine were in accord with recent reports of its action upon the vasomotor center and the blockade of sympathetic vasoconstriction in other regions.[11] In all cases where the clearance rate was changed, the change was in the direction of an increase. The interesting characteristics of the action of Hydergine were: (i) a latency between the infusion of the drug and the onset of an altered clearance rate, and (ii) a rhythmic fluctuation in the clearance pattern. The latency may reflect the time required for the drug to reach and maintain a specific concentration at its site of action before a response is elicited; or perhaps, it may be the time required for the drug to reach and penetrate certain receptor cells. The rhythmic fluctuations may be explained as a dynamic oscillation between the inherent constrictor tone of the blood vessels and the dilating tendencies of the drug.

The influence of Hydergine upon the electrical activity of the brain was quite the reverse of that seen with histamine. The EEG tracings suggested a decreased narcosis. To eliminate the possibility of other factors bringing about these electrical changes in response to histamine and Hydergine, carefully controlled experiments were performed in which the two drugs were infused alternately at twenty-minute intervals into the same animal over a period of at least one hour. In all cases the EEG tracings revealed a deepening narcosis during histamine infusion, the opposite effect with Hydergine.

SUMMARY AND CONCLUSIONS

We have described an application of a modified Kety tissue clearance technique which makes it possible to detect *changes* in the circulation through localized regions of the brain. Using this technique we have shown that infusion of histamine diphosphate into the carotid artery causes a diminished clearance from the internal capsule, while similar infusion of Hydergine causes an increase in clearance.

That these changes in clearance may be related to altered blood flow is further suggested by simultaneous changes in the EEG patterns.

REFERENCES

1. Boatman, J. B., Kendrick, T. R., Franke, F. R., and Moses, C.: The use of radioactive iodine, radioactive phosphorus, and radioactive sodium in the determination of cerebral and muscle clearance. J. Lab. clin. Med., 1950, *36*, 456.
2. Buchanan, T. J., Walls, E. W., and Williams, E. S.: Studies in radio-sodium clearance from the skin in man. Clin. Sc., Lond., 1954, *13*, 333.
3. Forbes, H. S.: Study of blood vessels on cortex of living mammalian brain—description of technique. Anat. Rec., 1954, *120*, 309.
4. Forbes, H. S., Wolff, H. G., and Cobb, S.: The cerebral circulation. X. The action of histamine. Amer. J. Physiol., 1929, *89*, 266.
5. Gibbs, F. A.: A thermoelectric blood flow recorder in the form of a needle. Proc. Soc. exp. Biol., 1933, *31*, 141.
6. Hyman, C., Rapaport, S. I., and Paldino, R.: Simultaneous multiple tissue clearances in measurement of trans-capillary diffusion rates. Amer. J. Physiol., 1950, *163*, 722.
7. Hyman, C., Stone, A., and Sosnow, M.: Application of tissue clearance technics in small animals. Proc. Soc. exp. Biol., 1953, *83*, 643.
8. Kety, S. S.: Measurement of regional circulation by the local clearance of radioactive sodium. Amer. Heart J., 1949, *38*, 321.
9. Kety, S. S.: Cerebral circulation in *Symposium on circulation and homeostasis*. Army Medical Service Graduate School. Walter Reed Army Medical Center, 1953, *3*, 180.
10. Kety, S. S.: Blood flow in muscle as measured by the clearance of a radioactive substance. *Ibid.*, p. 128.
11. Kety, S. S.: Personal communication.

12. Kety, S. S. and Schmidt, C. F.: The determination of cerebral blood flow in man by the use of nitrous oxide in low concentrations. Amer. J. Physiol., 1945, *143*, 53.

13. Ludwigs, N. and Schneider, M.: Uber den einfluss des halssympathicus auf die gehirndurchblutung. Pflugers Arch., 1954, *259*, 43.

14. McCall, M. L. and Sopp, T.: The clearance of radioactive sodium from the body and cervix of the human uterus as a measure of functional blood flow. Amer. J. med. Sc., 1951, *221*, 113.

15. McCall, M. L., Taylor, H. W., and Read, A. W.: The action of Hydergine on the circulation and metabolism of the brain in toxemia of pregnancy. Amer. J. med. Sc., 1953, *226*, 537.

16. Meyer, J. S., Fang, H. S., and Denny-Brown, D.: Polarographic study of cerebral collateral circulation. Arch. Neurol. Psychiat. (Chicago), 1954, *72*, 296.

17. Minard, D., Osserman, E. F., and Howell, S. R.: The lucite calvarium for direct observation of the brain in monkeys. Anat. Rec., 1954, *120*, 317.

18. Rapaport, S. I., Saul, A., Hyman, C., and Morton, M. E.: Tissue clearance as a measure of nutritive blood flow and the effect of lumbar sympathetic block upon such measures in calf muscle. Circulation, 1952, *5*, 594.

19. Schmidt, C. F.: *The cerebral circulation in health and disease*. Springfield, Charles C Thomas, 1950.

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SITE OF ORIGIN AND REFLEX BEHAVIOR OF POSTSYNAPTIC NEGATIVE POTENTIALS RECORDED FROM THE SPINAL CORD‡

In a previous paper[1] evidence has been offered that not only the intramedullary spike but also an early component of the following negative potential (labelled N_1a) is of presynaptic origin. N_1a was attributed to activity in afferent terminals. The present note deals with the site of origin

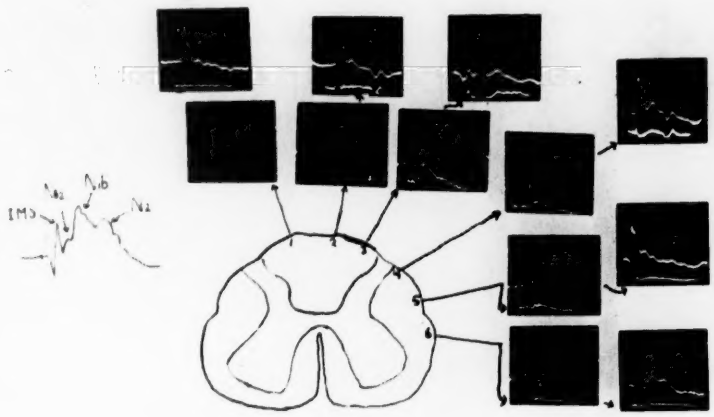

FIG. 1. Cat 11-11-54. Stimulus to internal saphenous nerve. All upper traces from point 1 on the ipsilateral side. Lower traces from contralateral points 2, 3, 4, 5, and 6 respectively. Time for inner ring of records: 1000 cycle; for outer ring: 60 cycle. Note that N_2 does not spread across cord.

of the postsynaptic negative components, N_1b, N_2, (a secondary wave cropping out from the descending limb of N_1b), and finally the late negative wave seen occasionally in decerebrate cats several milliseconds after the termination of the N_1 N_2 complex.[2] The technique employed is described in the earlier paper.[1]

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The site of origin of a potential may be readily determined by synchronous recording in two channels from a fixed ipsilateral lead and a contralateral lead shifted progressively around the cord. If there be no detectable difference in latency of either onset or crest of a wave in the two

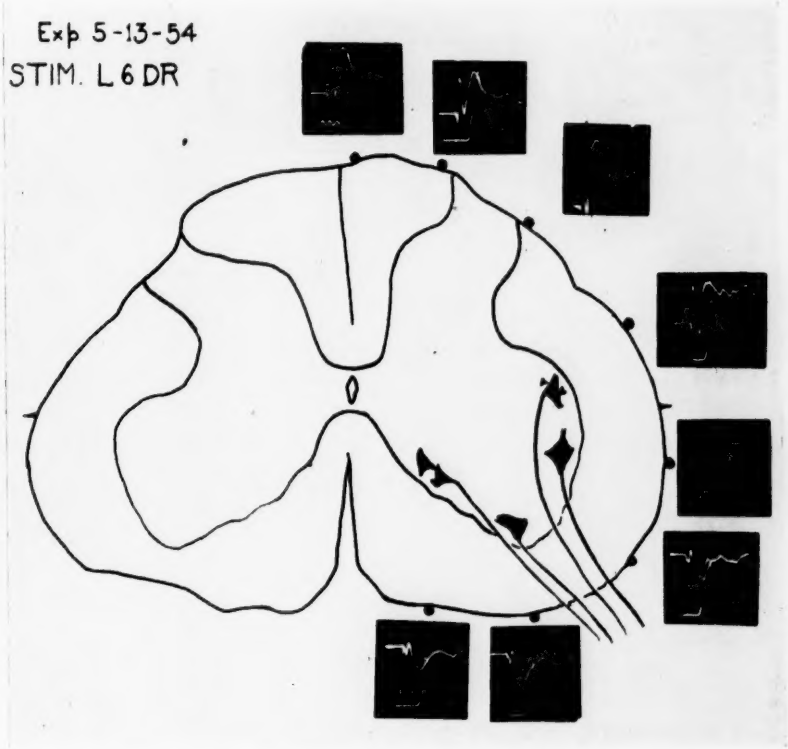

FIG. 2. Acute spinal cat. Upper trace from ipsilateral surface of cord. Lower trace from 6th lumbar ventral root. Stimulus to 6th lumbar dorsal root. Time in lower trace of mid-dorsal record: 1000 cycle. Note that in lateral leads N_2 is nearly as high as N_1.

records and if the potential be consistently greater on the ipsilateral side, it may be concluded that its source is ipsilateral and that the contralateral lead is in large measure recording spread of current from an ipsilateral source. Figure 1 indicates that such is the case for N_1b and N_2. The contralateral lead displays a small N_1 and no N_2 whatever. Such a result suggests a source for N_1 mesial to that for N_2. If this supposition be correct, ipsi-

lateral leads from the lateral aspect of the cord should show a relatively larger N_2 in relation to the size of N_1. Figure 2 shows that this is indeed the case.

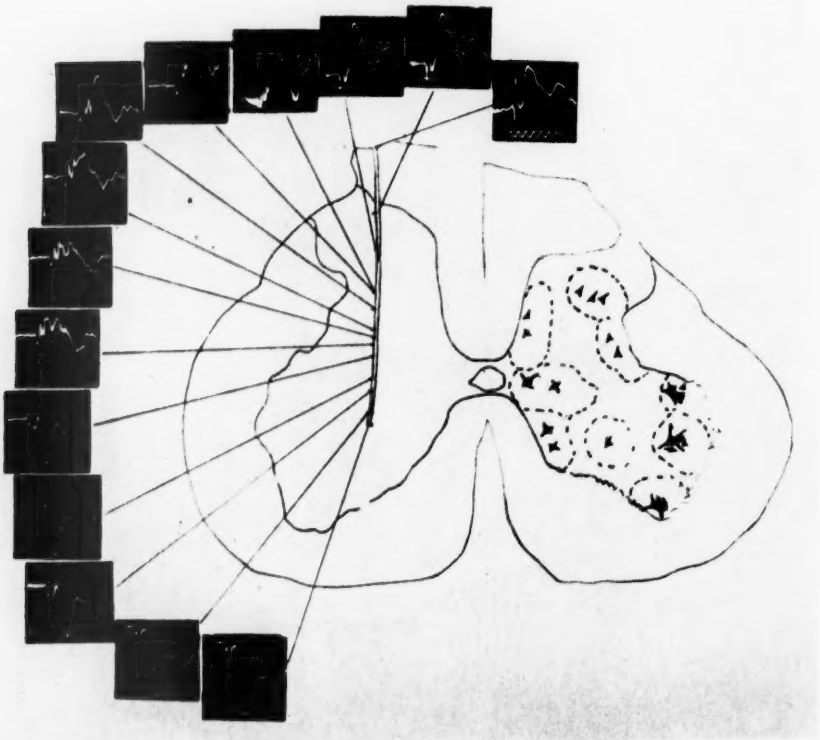

FIG. 3. Acute spinal cat. Stimulus to 6th lumbar dorsal root. Time (below surface record): 1000 cycle.

Assuming that these potentials are due to sinks in somata drawing current from sources in ventrally directed axons, a needle tip progressively driven ventrally through the cord should record a reversal from negativity to positivity when it passes the equator between the sources and sinks of the cells giving rise to the potential. In Figure 3, reversal occurs most dorsally for the early components of N_2 and more dorsally for the rest of N_2

than for N_1. At the base of the dorsal horn, N_1 has also reversed. It may be concluded that the site of N_1 extends deeper and more mesially in the dorsal horn than N_2. Consonant with the lateral location of N_2 is the fact that it is relatively larger in Figure 3 where the needle track passes through

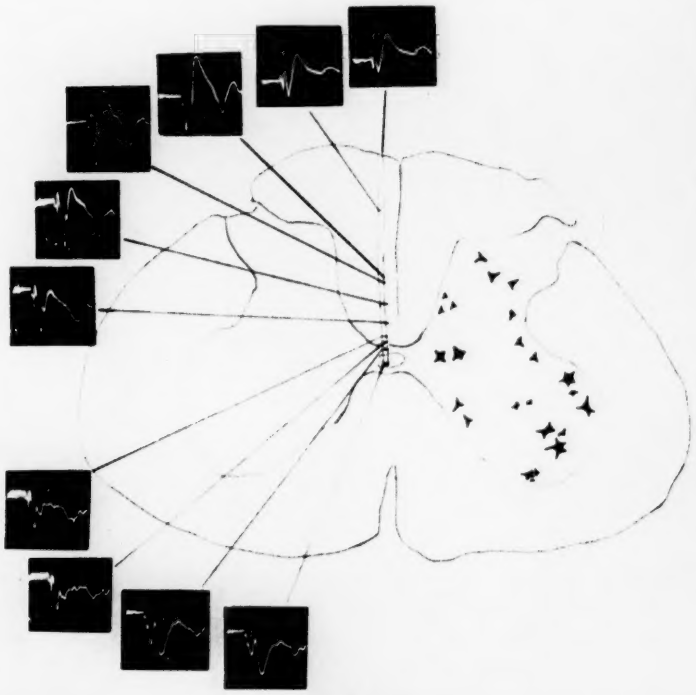

FIG. 4. From same experiment as Figure 3. Time record of Figure 3 applies also to Figure 4. Note that N_2 is lower than in Figure 3.

the dorsal horn than in Figure 4 where the track is near the midline. The approximate sources of these potentials are indicated in Figure 5.

Figure 6 records the late negative wave from a decerebrate cat in channels led from either side of the dorsum of the cord. In sharp contrast to N_1 and N_2 the late wave is definitely larger in the contralateral lead. Its contralateral origin, its time relations, and its recruiting form suggest that it may be concerned with the crossed extensor reflex.

Turning to the reflex relations of the earlier waves, N_1 is far more resistant to inhibition than is N_2, whether from an ipsilateral (Fig. 7) or a contralateral source (Fig. 8, top row). In Figure 7, N_1 is slightly reduced, N_2 is completely inhibited at all intervals recorded. The polysynaptic reflex is commensurately reduced in the portion contemporaneous with N_1 and completely inhibited in the portion contemporaneous with N_2.

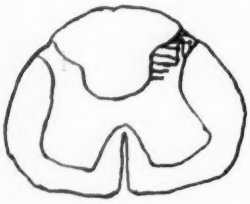

FIG. 5. Horizontal lines indicate probable region of origin of N.b, vertical lines that of N_2.

The top row of Figure 8 illustrates partial inhibition of an ipsilateral reflex from a crossed source in a chronic spinal cat. Stimulation is a single strong pulse to the sciatic nerve of each side. N_1 is reduced, N_2 obliterated, the early polysynaptic reflex reduced commensurately with N_1 and the portion synchronous with N_2 completely inhibited. In the second and third rows amplification of the ventral root potential is increased. Row 2 shows an ipsilateral and two crossed reflexes illustrating the range in the crossed reflex response. Row 3 is devoted to ipsilateral inhibition of the crossed reflex. In the first of these there is no change in the cord potential, in the second and third, a slight reduction. In all three, there is complete inhibition of the crossed reflex. The conclusion is obvious. Crossed inhibition of the ipsilateral reflex is largely mediated in the dorsal horn; ipsilateral inhibition of a crossed reflex is dominantly located in the ventral horn.

DISCUSSION

Our localization of the site of N_1 agrees with that obtained by Lindblom and Ottosson[8] who injected small amounts of osmic acid at various points in the cord. We are not aware of any previous localization of N_2 or of the late negative wave.

The reflex rôle of N_1 demonstrated by Hughes and Gasser[6] and by Hughes, McCouch, and Stewart[7,10] has been disputed by Bernhard and Widén[2,3,4] on the ground that it is not inhibited by low threshold units in crossed cutaneous nerves; that increase in stimulus strength increases reflex response linearly but increase in N_1 follows a parabolic curve; and that conditioning by an antidromic volley in the dorsal columns facilitates the reflex while inhibiting N_1.

We quite agree that much stronger stimuli are required to obtain crossed inhibition and that it is often unobtainable in acute preparations with little or no positive wave.[5,7] The lack of identity in rate of increase of reflex and

cord potential may be attributed to two factors: (1) the contribution to the cord potential of postsynaptic potentials in subliminally stimulated interneurons and (2) the fact that deeper elements are not so well recorded from the dorsum of the cord as superficial ones. Conditioning from the dorsal columns appears to offer a more serious objection. Measurement of the records in their experiment suggests, however, that the facilitated response is monosynaptic. A trace of a greatly inhibited polysynaptic reflex

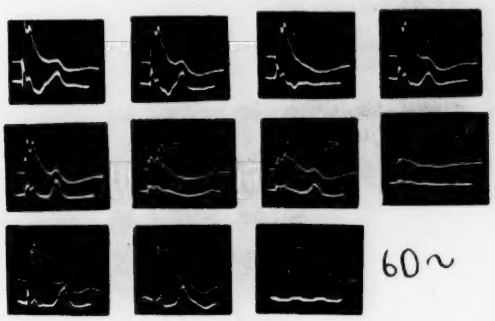

FIG. 6. Decerebrate cat: Stimulus to 6th lumbar dorsal root. Upper trace from ipsilateral dorsal surface; lower trace from contralateral dorsum. Note that the late negative wave is larger on the contralateral side. Time: 60 cycle.

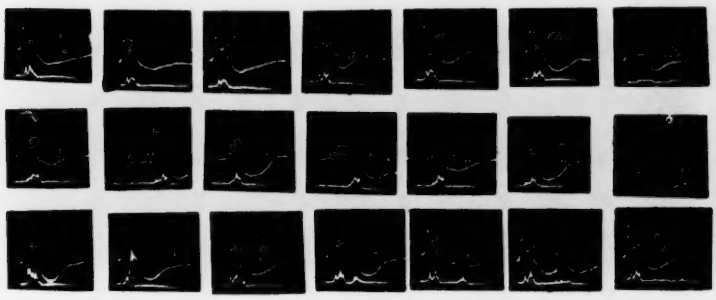

FIG. 7. Acute cat. Sixth lumbar dorsal root split into two strands; conditioning shock to one, test shock to the other. Upper row: conditioning alone. Middle row: test alone. Lower row: both. Upper trace from ipsilateral dorsum of cord. Lower trace from 6th lumbar ventral root. Time (lower trace in last record of top row): 60 cycle. Note prolonged inhibition of N_1 and of portion of reflex response contemporaneous with it.

may be seen following it. Here, as in our records, the inhibition of the polysynaptic reflex is proportional to that of the reflex response.

We question whether it is possible to dissociate interneurons giving origin to ascending pathways from those mediating reflex activity. It seems highly probable that the axons running up the cord give off collaterals

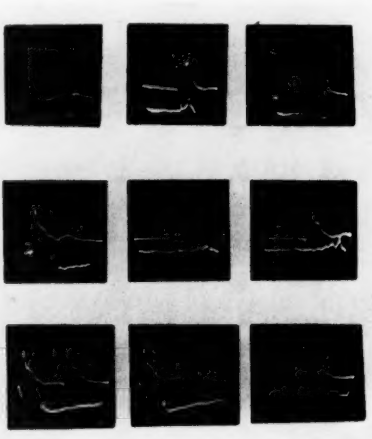

FIG. 8. Cat with transection of cord 80 days previously. Stimulus to sciatic nerve of each side. Upper tracings: potentials from ipsilateral dorsum of cord; lower tracings from 6th lumbar ventral root. Top row: contralateral conditioning of ipsilateral reflex. Note similar degree of inhibition of cord and root potentials. Middle and lower row with higher amplification of root potentials. Middle row: ipsilateral reflex and 2 crossed reflexes to show range of crossed response. Lower row: ipsilateral conditioning of crossed reflex. Note the virtually complete inhibition of the root potential with little or no reduction of the cord potential. Time: 60 cycle.

which course to the ventral horn to excite or inhibit motoneurons. The finding that N_2 is highly susceptible to inhibition merely confirms a much earlier observation by Hughes and Gasser.[8]

SUMMARY

The negative intermediary potential, N_1b, arises in the mesial portion of the ipsilateral dorsal horn including the region near its base.

N_2 arises in the lateral portion of the ipsilateral dorsal horn at a site which does not extend so far ventrally as that of N_1b.

The late negative wave seen occasionally in decerebrate preparations arises in the contralateral dorsal horn. Its threshold is somewhat higher

than that of N_1b. Its time relations and recruiting form suggest an association with the crossed extensor reflex.

N_1b and N_2 are associated with the ipsilateral flexor reflex. N_1b is far more resistant to both ipsilateral and crossed inhibition than is N_2.

Inhibition of the ipsilateral flexor reflex occurs largely in the dorsal horn whether the source of inhibition be ipsilateral or crossed.

Ipsilateral inhibition of the crossed reflex is dominantly in the ventral horn.

REFERENCES

1. Austin, G. M. and McCouch, G. P.: Presynaptic component of intermediary cord potential. J. Neurophysiol., 1955, *18*, 441-451.
2. Bernhard, C. G.: Analysis of the spinal cord potentials in leads from the cord dorsum. In: *The spinal cord* (Ciba Symposium). Boston, Little Brown & Co., 1953, 43-60.
3. Bernhard, C. G.: The cord dorsum potentials in relation to peripheral source of afferent stimulation. Cold Spring Harbor Symposia on Quantitative Biology, 1952, *17*, 221-232.
4. Bernhard, C. G. and Widén, L.: On the origin of the negative and positive spinal cord potentials evoked by stimulation of low threshold cutaneous fibers. Acta. physiol. scand., 1953, *29*, Suppl. 106 (in honor of S. Ramón y Cajal) 42-54.
5. Hughes, J. and Gasser, H. S.: Some properties of the cord potentials evoked by a single afferent volley. Amer. J. Physiol., 1934, *108*, 295-306.
6. Hughes, J. and Gasser, H. S.: The response of the spinal cord to two afferent volleys. Amer. J. Physiol., 1934, *108*, 307-321.
7. Hughes, J., McCouch, G. P., and Stewart, W. B.: Cord potentials in the spinal cat. Amer. J. Physiol., 1937, *118*, 411-421.
8. Lindblom, U. F. and Ottosson, J. O.: Localization of the structure generating the negative cord dorsum potential evoked by stimulation of low threshold cutaneous fibers. Acta. physiol. scand., 1953, *29*, Suppl. *106*, 180-190.
9. McCouch, G. P., Hughes, J., and Stewart, W. B.: Crossed inhibition of the flexor reflex in the spinal mammal. J. Neurophysiol., 1941, *4*, 547-554.

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HIPPOCAMPAL FUNCTION: TENTATIVE CORRELATIONS OF CONDITIONING, EEG, DRUG, AND RADIOAUTOGRAPHIC STUDIES‖

And are we too bold in expressing the hope that . . . we may one day be able to bring mental experience and physiological experience into harmonious and meaningful juxtaposition? J. F. Fulton: *Functional Localization in the Frontal Lobes and Cerebellum*, The William Withering Memorial Lectures, 1948.

In this volume honoring Dr. Fulton, it is fitting to call attention to his great contribution to the study of functional localization in the brain. It is of consequence to research on mental disease, our country's foremost health problem, that long ago his interest in localization not only applied to the representation of bodily functions, but also transcended Sherringtonian tradition and extended to psychological processes. His use and promotion of interdisciplinary study for demonstrating correlations of brain function and psychological phenomena set the stage for lines of endeavor that promise to be fruitful for years to come.

During the past two decades investigations conducted in Dr. Fulton's laboratory and elsewhere have gone far in substantiating a postulated dichotomy in the function of the phylogenetically old and new cortex.[20, 14] This "schizophysiology"[10] has fundamental implications for psychology and psychiatry because it bears on distinctive attributes of emotional and intellectual behavior. It also has immediate relevance to "psychomotor" epilepsy.

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The structural basis for the foregoing dichotomy was implicit in the anatomical findings of Broca. In 1878, he demonstrated that a large convolution which he called the great limbic lobe is found as a common denominator in the brains of all mammals.[1] The structural constancy of this primitive convolution stands in contrast to the rapidly evolving neocortex which mushrooms around it. The greater part of the phylogenetically old cortex is contained in the great limbic lobe. This cortex together with its subcortical cell stations comprises a functionally integrated system which may be appropriately referred to as the limbic system (see ref. 15 for terminology). Experiment has shown that various forms of visceral-somatic and emotional behavior are dependent on this system, whereas problem-solving behavior is largely determined by the neocortex and its associated structures (see ref. 5).

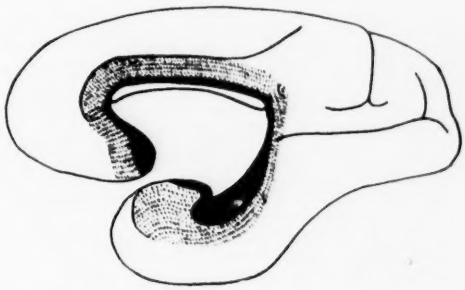

FIG. 1. Drawing of medial surface of macaque's brain, showing schematically that the limbic lobe contains two concentric rings of phylogenetically old cortex. The archicortex (black) makes up the inner ring, and the greater part of the mesocortex (stipple) is found in the outer ring. In evolution, the archicortex is stretched out by the growth of the corpus callosum so that in higher forms the bulk of it is folded into the hippocampal formation in the inferomedial part of the temporal lobe.

This paper will present some tentative correlations based on diversified studies on the hippocampus that are in progress and bear on the problem of functional localization in the limbic system.

As diagrammatically illustrated in Figure 1, the hippocampus is a large convolution comprising the greater part of the so-called archicortex which forms the innermost portion of the limbic lobe. In evolution, with the growth of the corpus callosum, it is pulled out somewhat like a piece of chewing gum so that in higher forms the bulk of it comes to lie within the inferomedial part of the temporal lobe. It is to be emphasized that the hippocampus has the structural features of the most primitive type of cortex and that in development it bears a more intimate relationship to the hypothalamus than the cortex that differentiates at a later time in phylogeny.

One of the most striking demonstrations of the neural integration of limbic structures and the potential schizophysiology of limbic and neocortical systems is provided by mapping the spread of an afterdischarge induced

in the hippocampus. As shown by Kaada[10] and others,[2] such discharges have a tendency to spread throughout and be largely confined to the limbic system and perilimbic structures. It is striking to find that intense seizure activity may propagate in the limbic system without resulting in an appreciable alteration of the electroencephalogram recorded from the outer convexity of the neocortex.[18]

There are grounds for inferring that propagating seizures induced either electrically or chemically in the hippocampus result in what must amount, in part, to a functional ablation of the limbic system. Theoretically, therefore, the study of intact waking animals during hippocampal seizures provides a means of assessing the effect of the deprivation of limbic function on behavior.

A general description of the behavior of an animal during a hippocampal seizure will provide background for presenting the conditioning, electroencephalographic, drug, and radioautographic studies to be summarized. It must be emphasized first of all that despite the intense nature of the seizure recorded electrically, there is generally little or no evidence of it in the skeletal musculature. Convulsive activity, if present, usually involves the ipsilateral face. Sometimes there is gagging, retching, or salivation. A number of the spontaneous or induced behavioral changes during hippocampal seizures are reminiscent of those seen in animals deprived of the forebrain. One is impressed by the animal's lack of spontaneity of movement and its seemingly poor contact with its environment. There is an apparent incapacity for directed appropriate action in response to various stimuli. Although the reverse may happen occasionally, there generally appears to be underreactivity to painful stimuli of moderate intensity. Intense noxious stimulation, however, elicits a state resembling sham rage that is abruptly followed by the animal's assumption of prolonged catatonic-like stances when such stimulation is terminated. One can demonstrate the retention of a number of postural and viscerosomatic reflexes.

CONDITIONING STUDIES

The injection of microamounts of crystalline carbachol into the hippocampus results in a prolonged seizure during which one can observe for an hour or more the type of changes that have been described.[18] Taking advantage of this method, we undertook to obtain an objective measure of whether or not an animal is deprived of the capacity for directed, appropriate action during a drug-induced hippocampal seizure.[23, 18] Several cats and one squirrel monkey were conditioned to avoid a shock following the sound of a buzzer by crossing from one side of a cage to the other. At the time the

seizure was reaching its height, these animals no longer responded appropriately to the conditioned stimulus. They appeared confused and moved about at random. Upon receiving the unconditioned stimulus, however, they might at times (perhaps accidentally as the result of random, violent jumping) reach the other side with greater alacrity than in the test under normal conditions. Finally at the very height of the seizure, they might appear almost unresponsive or hop around in all directions.

The conditioned escape situation requires bodily orientation and a complex sequential relation of reflexes. It was, therefore, of interest to ascertain whether or not a hippocampal seizure would also alter or abolish such relatively simple conditioned reflexes as a foreleg response or a change in the cardiac rate. This question also bore on another problem. Gantt has observed that a conditioned cardiac reflex may persist in an animal long after a somatic reflex conditioned by the same stimulus has become extinguished.[6] He refers to this condition as *schizokinesis*. The foregoing experiments, therefore, provided an opportunity to obtain a clue as to whether such a schizokinesis was in any way related to the schizophysiology of the limbic and neocortical systems. In other words, it was sought to discover whether or not a hippocampal seizure would have a differential effect on conditioned somatic and cardiac responses. This investigation has not reached a stage where it can answer these questions, but a number of experiments have demonstrated fairly conclusively that a hippocampal seizure may abolish or markedly alter conditioned cardiac and respiratory responses.

In the exploratory experiments on cats to be described here, classical trace conditioning was used.* This choice was based on the assumption that the interval between the conditioned and unconditioned stimuli would bring to the fore differential changes in the heart rate and respiration that would not otherwise be so apparent. Although after an extensive number of trials no foreleg response was obtained by this method, conditioned cardiac and respiratory changes were readily elicited, and this provided a means of testing the effect of hippocampal seizures on these aspects of conditioning. The conditioned stimulus was an interrupted sound and the unconditioned stimulus a shock to the foreleg. As illustrated in the left-hand records in Fig. 2, the conditioned stimulus was typically followed by some slowing of the heart and by shallow and more rapid respiration. It is important to emphasize that the animals remained quiet during the interval between the

* These investigations have thus far involved 13 animals. It should be emphasized that one must wait around 5 minutes between trials if one is to be successful in establishing consistent cardiac and respiratory responses in the cat. The animals are trained to remain quiet in a restraining device.

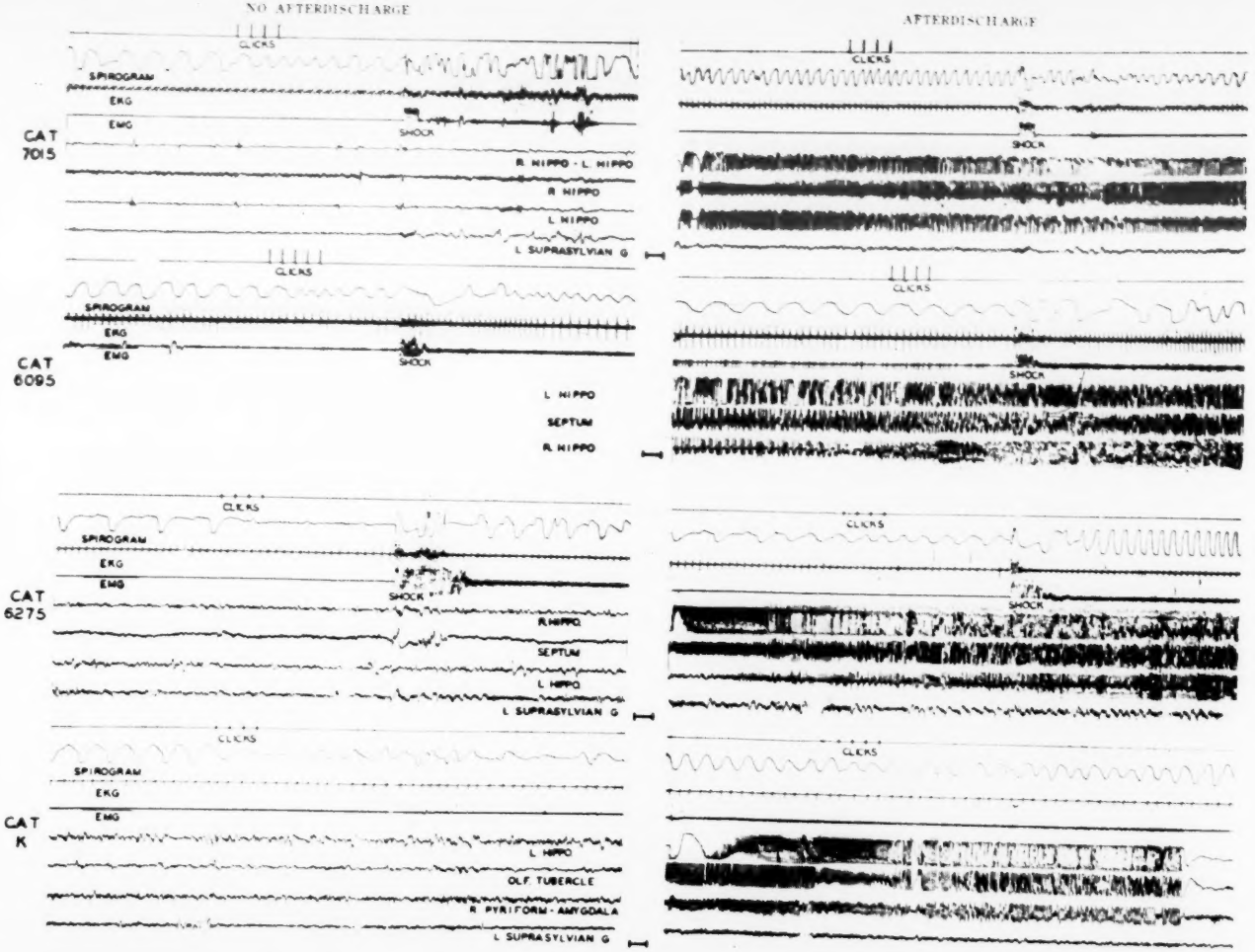
NO AFTERDISCHARGE
AFTERDISCHARGE
CLICKS
SPIROGRAM
EKG
EMG
SHOCK
CAT 7015
R. HIPPO - L. HIPPO
R. HIPPO
L. HIPPO
L. SUPRASYLVIAN G
CAT 6095
L. HIPPO
SEPTUM
R. HIPPO
CAT 6275
R.HIPPO
SEPTUM
L. HIPPO
L. SUPRASYLVIAN G
CAT K
L. HIPPO
OLF. TUBERCLE
R. PYRIFORM - AMYGDALA
L. SUPRASYLVIAN G

Fig. 2.

conditioned and unconditioned stimuli because one was thereby assured that the resulting cardiac and respiratory responses were not attributable to diffuse bodily movements. Once these responses were established, the animals were tested during hippocampal seizures induced by electrical stimulation. There were many instances such as are illustrated in the first and second records of Fig. 2 where during the seizure there was no appreciable alteration of respiration or heart rate following the conditioned stimulus, although the animal was able to respond to the shock. In other instances, such as illustrated in the third record, where there were clearly detectable changes in respiration, these did not begin to approach the picture seen in the absence of seizures. Not indicated in the records, but of considerable interest, was the alteration of the animals' vocal response to the unconditioned stimulus during the hippocampal afterdischarge. The plaintive meowing that ordinarily followed the shock was replaced by growling and hissing. It is also significant to point out that when single muscle units happened to reveal themselves in the electromyogram, there was no change in the rate of their discharge during the onset and continuation of the seizure.

EFFECT OF RESERPINE ON CONDITIONING

Reserpine is now extensively used for the treatment of psychiatric and cardiovascular disorders. In the course of this work, observations have been made that point to certain parallels between the behavior of the reserpine-treated animals and those subjected to seizures induced by the local application of carbachol to the hippocampus. In both situations, the animal manifests a poverty of spontaneous movement, underreactivity to painful stimuli, and a failure to direct its attack when the experimenter applies intense noxious stimulation. A further parallel is suggested by experiments in which we have administered reserpine to cats in which consistent conditioned cardiac and respiratory changes had been established.* It has been

* Reserpine (Serpasil) was administered parenterally in a dose of 1 mg/kg. We are grateful to Ciba Pharmaceutical Products for providing the Serpasil used in these experiments.

FIG. 2. Excerpts from records of 4 cats, comparing respiratory and cardiac responses to a conditioned stimulus during the usual test situation (left-hand records) and during hippocampal afterdischarges (right-hand records). When the cat is held in a restraining device and trace conditioning is employed, the conditioned stimulus (clicks) is typically followed by some slowing of the heart and by shallow and more rapid respiration. See text for further description.

EKG, electrocardiogram. EMG, electromyogram from the leg receiving the shock. Horizontal calibrations correspond to one second.

found that one to four hours after the parenteral administration of the drug, these responses are no longer elicited.

ELECTROENCEPHALOGRAPHIC STUDIES

In an electroencephalographic study comparing the effects of various neuropharmacological agents on the limbic and neocortical systems, we have administered reserpine to 11 cats.[11,12] The results of these experiments are also suggestive that a number of the behavioral changes seen in reserpine-

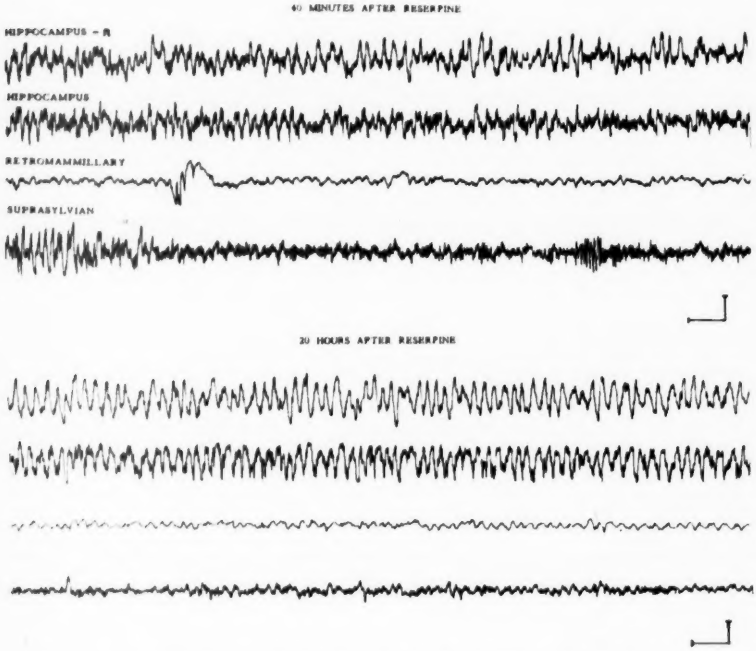

FIG. 3 Excerpts from the EEG of a cat at 40 minutes and 20 hours after the administration of reserpine. The upper record may be considered as typical of what one observes under normal conditions. The regular activity seen in the hippocampus appeared after the experimenter called, "Kitty, kitty." In contrast it is noted that the EEG from the suprasylvian gyrus simultaneously became "desynchronized." Lower record illustrates that by the 20th hour after reserpine slow rhythmic activity may be practically continuous in the hippocampus during long periods when desynchronized activity of the waking state is recorded from the neocortex. The record is also illustrative of the rhythmic activity which may be manifest in the region of the posterior hypothalamus and which appears to be synchronous with that seen in the hippocampus. All recordings bipolar except uppermost tracing. R, reference electrode. Horizontal and vertical calibrations correspond, respectively, to one second and 200 microvolts.

treated animals and those subjected to hippocampal seizures are attributable to alteration of function in comparable neural structures. About four hours after the administration of the drug, the recording from the hippocampus begins to show a good deal of rhythmic activity at a frequency of 3.5 to 4 cycles per second. This activity is conspicuous only during periods when desynchronized activity of the waking state is recorded from the neocortex. During the next several hours, rhythmic activity becomes much more conspicuous and develops a slower frequency that usually ranges from 2.5-3.5 cycles per second. As illustrated in Figure 3, by the 20th hour rhythmic activity may be practically continuous in the hippocampus during long periods when desynchronized activity of the waking state is recorded from the neocortex. The record is also illustrative of the rhythmic activity which may be manifest in the region of the posterior hypothalamus and which appears to be synchronous with that seen in the hippocampus. During the long period when the animal is recovering from the effects of reserpine, one sees a gradual reversal in the course of the electroencephalographic events that have been described. The changes in the heart rate follow a similar time course, there being first a progressive slowing followed by a gradual return to the normal rate. The simultaneous recording of the electroencephalogram and the electrocardiogram gives assurance that the rhythmic activity recorded from the brain is not attributable to a pulsation artefact.

It has been curious to find that except for the extended time course, the electroencephalographic picture associated with reserpine has many similarities to that observed during the induction and recovery stages of ether anesthesia. Of the agents we have tested, ether and reserpine are the only ones that have been associated with this distinctive type of electroencephalogram.* This suggests that ether and reserpine share some action in common in regard to their effect on hippocampal-hypothalamic function, which by inference is depressant in nature.

RADIOAUTOGRAPHIC STUDIES

The foregoing inference would be compatible with the findings of radioautographic studies employing S^{35} labeled l-methionine.[1] The results of this work will be more clearly understood if the nature of these experiments is briefly described. As methionine is an essential amino acid, it is incorporated into protein when administered to an animal. Hence the rate of incorporation of S^{35} after the administration of S^{35}-labeled l-methionine serves as an

*It has since been found that when an animal breathes CO_2, the activity of the hippocampus becomes very regular, but in the few observations that have been made thus far, it has been noted that the frequency of the rhythmic potentials is somewhat faster than in the conditions under consideration.

index of the rate of synthesis of respective proteins. Guided by this knowledge, we undertook to learn the fate of the radiosulphur in the brain under normal conditions, as well as in situations where an animal was subjected to infection, convulsions, or treatment with various drugs. The labeled methionine (specific activity around 25 microcuries per milligram) was administered intraperitoneally to rats in the amount of 4 milligrams. The time of administration varied according to the demands of the experiment. Except for the variable under investigation, the experimental conditions were the same for the control and experimental animal. Sacrifice was car-

FIG. 4. Radioautographs of comparable brain sections from a control and two reserpine-treated rats. Sections cut simultaneously and mounted together to insure they would be of equal thickness and subject to identical photographic processing. Rat, whose radioautograph is shown at right, received reserpine on 3 and 1 days prior to administration of S^{35}-labeled l-methionine. The other treated animal (left side of figure) received a single dose on the day before. Section from control is shown in middle. See text for further description.

ried out by clearing the circulatory system of blood after the animal had been rapidly anesthetized with ether. The brain was fixed *in situ*. The brains of a control and one or more experimental animals were so mounted that comparable transverse sections could be obtained on one cutting and mounted on a single slide. This insured radioautographic comparison of sections of equal thickness as well as identical photographic processing. Sections were usually cut at 15 microns and exposed by contact to X-ray film for periods generally not exceeding a week. Subsequently, the sections were stained either with thionine or gallocyanin.

In control experiments, well-differentiated radioautographs were obtained from rats sacrificed within the first hour following an injection of the isotope. Electrophoretic studies of the blood serum revealed that almost all of the radioactive sulphur remaining in the blood at the end of one hour was incorporated into blood proteins. As briefly reported elsewhere,[17] radioautographs obtained in this manner show depths of contrast that bear a striking resemblance to Nissl-stained sections (cf. right-hand radioautograph of Fig. 5). Accordingly, one finds the following parallels: (1) The radio-

activity manifests itself predominantly in the grey matter. (ii) *The limbic cortex, generally, and the hippocampal formation, in particular, appear darker in the radioautograph than the neocortex.* (iii) The cerebellar cortex is also conspicuously dark. (iv) In correspondence with their deep coloration in Nissl, such subcortical structures as the supraoptic, paraventricular, and tuberal nuclei of the hypothalamus, the anterodorsal and medial habenular nuclei of the thalamus, the interpeduncular nucleus of the midbrain, etc., appear darker in the film than other nuclear formations. The pituitary and pineal glands, as well as the choroid plexus and ependymal lining, appear black in the film.

FIG. 5. Radioautographs of comparable sections from hemispheres of a control (right) and a convulsed animal (left). Sections cut simultaneously and mounted together to insure they would be of equal thickness and subject to identical photographic processing. The experimental animal had insulin-induced convulsions for an hour prior to the administration of S^{35}-labeled l-methionine. Its brain shows considerably less radioactivity than the control's. In contrast to the control, note that the region of the hippocampus is as pale as the neocortex. Curiously enough, in this instance the pyriform cortex and perithalamic reticulum were not affected to the same degree as other parts of the brain.

It has been found that radioautographs from rats treated with reserpine show a generalized decrease in radioactivity as compared with the controls. This is illustrated in Figure 4 which compares the radioautographs from a control and two treated animals. The one at the right of the figure is from a rat that received reserpine (Serpasil) in a dose of 1 mg./kg. on one and three days before the administration of S^{35}-labeled l-methionine. It is considerably paler than that from an animal receiving a single dose (left radioautograph) which in turn is less intense than the control (middle of figure).

The picture in the case of reserpine is essentially similar to what one finds after inducing deep anesthesia in an animal. It might be inferred therefore that reserpine, like anesthesia, interferes with processes that lead to protein synthesis in the nerve cells of the brain. The qualitative appraisal of the radioautographs not only suggests that the changes resulting from this interference are generally manifest in the grey matter, but also that they are relatively greater in structures ordinarily showing a high degree of radioactivity. Such differential effects have been most clearly seen in radioautographs from animals suffering from infections, or, as illustrated in Figure 5, subjected to a series of convulsions by means of insulin. In the

figure, a section through the hemisphere of a convulsed animal is shown on the left and a comparable section from the control on the right. It is seen that the film in the region of the hippocampus of the convulsed animal is as pale as that in neocortical areas. In the light of these observations, the possibility is suggested that such a structure as the hippocampus would stand in a position to be more readily affected than other parts of the brain by conditions interfering with protein synthesis. If this were true, it would perhaps contribute a partial explanation of the electroencephalographic changes that have been described above and provide another clue as to one of the sites of action of reserpine.

DISCUSSION

The foregoing studies have presented diverse experimental evidence indicating that derangement of function in the hippocampus and closely related structures results in measurable changes in the psychological behavior of animals.* It is obvious, however, that much more experimentation will be necessary before one can more than speculate about *how* the structures under consideration influence psychological processes. Of the many distinctive properties of the hippocampus its peculiar bioelectrical activity comes nearest at the present time to giving a clue as to the manner in which this primitive, enigmatic convolution affects cerebral function. After a brief review of the nature of this activity, it will be of interest to consider it in the light of some of the findings of the conditioning experiments that have been described in this paper.

Electrophysiological studies have shown that, in addition to brief responses, stimulation by way of various intero- and exteroceptive systems results in prolonged trains of rhythmically recurring potentials in the hippocampal gyrus and the hippocampus.[9, 10, 7, 8] Figure 6, showing a record taken from a conditioning experiment, illustrates the nature of the rhythmic activity that is evoked in the hippocampus by sensory stimulation. It has been emphasized that such responses in the hippocampus are readily abolished by small doses of barbiturates.[7] A similar type of rhythmic activity also occurs spontaneously in the hippocampus at times when an animal appears to shift or focus its attention or to become alerted.[12, 13, 8] Green and Arduini infer that this activity is dependent on the "reticular activating system" of the brain stem and state that it may be induced in the hippocampus by "arousing stimuli" that are too weak to affect the neocortex.[8] In our own experience, painful stimuli are particularly effective in eliciting

* The relevance of such findings to clinical problems has been touched upon elsewhere.[16, 18]

perseverating rhythmic activity in the hippocampus, and it can be shown that when so induced, it may outlast the desynchronized activity (low voltage, random, fast activity) that appears in the neocortex.[2]

The question arises as to whether or not the foregoing bioelectrical findings are in any way related to differences we have observed in trying to establish conditioned somatic and autonomically dependent responses by

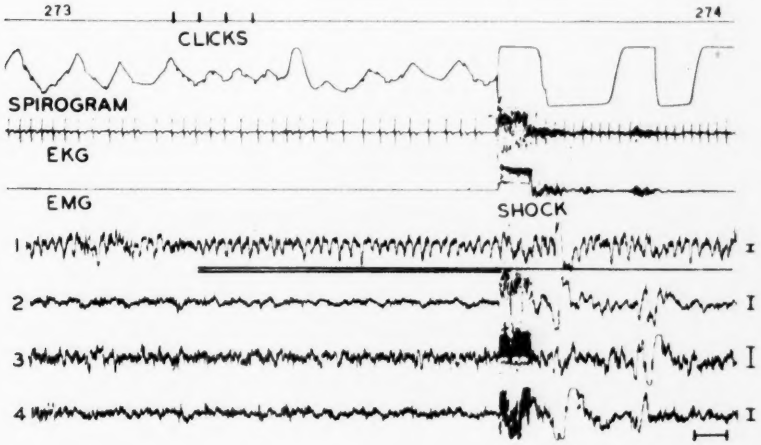

FIG. 6. Record from cat in process of training by "trace" conditioning. Underlined section of tracing labeled #1 illustrates nature of perseverating rhythmic activity appearing in posterior part of body of hippocampus following sensory stimulation. Note how it lasts through the interval between cessation of CS (clicks) and onset of US (shock) and continues subsequently. Cat still undergoing testing so that sites of electrodes have not been confirmed histologically. Tracing #1 from bipolar electrodes intended for posterior hippocampus; #2, right anterior hippocampus; #3, septum; #4 ectosylvian gyrus. EKG, electrocardiogram. EMG, electromyogram from leg receiving shock. Horizontal calibration, 1 second; vertical calibration, 100 microvolts.

"trace" and "delayed" conditioning. In the preliminary investigations described here, "trace" conditioning was used. This form of conditioning was chosen because of the assumption that the interval between the application of the conditioned and unconditioned stimuli would bring to the fore changes in the heart rate and respiration that would not otherwise be so apparent. In the case of the cat, this proved a fortunate choice insofar as the animal remained quiet during the interval, and this gave assurance that the resulting cardiac and respiratory responses were not attributable to diffuse bodily movement. As was pointed out, the animals readily developed conditioned cardiac and respiratory responses, but no foreleg response in

spite of numerous trials. On the other hand, if one employs "delayed" conditioning, as we are currently doing in a continuation of this investigation, the foreleg response is quickly established. It should be emphasized that in "trace" conditioning there is an interval of several seconds between the cessation of the conditioned stimulus and the onset of the unconditioned stimulus, whereas in "delayed" conditioning the conditioned stimulus overlaps in time the unconditioned stimulus.

How is one to account for the fact that in the test situation that calls for the association of two temporally separated events, the cardiac and respiratory responses are readily conditioned whereas the foreleg response is not? In other words, how is one to explain the fact that learning in this case appears to impress itself more readily on the heart and lungs than on the leg that receives the shock? The hippocampal formation is intimately related to the hypothalamus. Is it possible that the residual neural perturbations remaining in these structures following sensory stimulation (see Fig. 6) allow a more ready association of two separated events than is possible in the neocortex where one does not see a comparable phenomenon? If this were so, it would provide a possible explanation of how two separated events are so related as to impress themselves more readily on the activities of the viscera than on the discriminative acts of the somatic musculature that are presumably dependent on the neocortex. In a similar fashion, it would help to explain why conditioning methods involving an overlap in time of the conditioned and unconditioned stimuli are more conducive to establishing conditioned somatic responses than "trace" conditioning. If such deductions are borne out by further experimentation, they would have important implications for learning theory as well as possibly for formulations of dynamic psychiatry in regard to the childhood incipience of psychosomatic disorders.*

* Some illustrations may be taken from the discussion in a paper presented at a Symposium on Neurovascular Relationships, Annual Meeting of the Council for High Blood Pressure Research, American Heart Association, Cleveland, Ohio, November 19, 1955.

One knows, for example, that in the house training of a dog one must punish the animal almost instantly after it soils or it will fail to learn the significance of the punishment and may subsequently assume a cowering attitude every time it sees its master. In other words, it fails to discriminate that the only time it needs to fear the hand of authority is when there has been a specific misdeed. Pavlov observed that, after establishing a reflex by trace conditioning, the animal might show the reflex in response to many different stimuli. In human affairs, a number of examples come to mind of situations that might lead to a comparable generalization. There is the situation, for example, where a mother habitually postpones punishment of a child until the father can administer the whipping. Is it not possible that such trace conditioning would be conducive to the establishment of indiscriminate visceral reactions in childhood? In the case mentioned, through the symbolic process, the father would stand in the position to become interchangeable with all authoritative figures who in turn are

The foregoing formulation would be compatible with inferences we drew in reporting the reserpine studies, as well as with observations reported by others concerning the effects of bilateral ablation of the hippocampal formation. Pribram has found in monkeys that bilateral ablation of the hippocampus results in rapid extinction of postoperatively acquired conditioned avoidance.[21] Scoville has observed profound memory disturbances in patients following bilateral excision of the hippocampal formation.[22]

There is at present no ready explanation of what accounts for the persisting bioelectrical changes that can be evoked in the hippocampus. Perhaps they are partly to be explained by avalanche conduction along small fiber systems feeding into it. Some evidence from experiments that are yet to be published suggests that a persistent action of a neural transmitter (presumably acetylcholine or like acetylcholine) that is released upon afferent stimulation may be another contributing factor.

SUMMARY

Past investigations have indicated a dichotomy in the function of the phylogenetically old and new cortex. This dichotomy has important implications for psychology and psychiatry because it bears on distinctive attributes of emotional and intellectual behavior. This paper deals with studies seeking a further elucidation of the psychophysiological rôle of the "old" cortex which is now recognized to be fundamentally involved in viscerosomatic and emotional functions. The greater part of the old cortex is contained in the limbic lobe. Together with its subcortical cell stations, it comprises the limbic system.

A seizure that is induced either electrically or chemically in the hippocampal formation has the tendency to spread throughout and be largely confined to the limbic system. There are grounds for inferring that this results in what must amount *in part* to a functional ablation of the limbic system. Theoretically, therefore, the study of intact waking animals during

to be feared regardless of the circumstances in which they appear. The psychosomatic implications of this kind of surmise in regard to the cardiovascular system do not need to be belabored here. Most significant in another respect, and based on very extensive observations, are Gantt's findings that a conditioned cardiac reflex may persist long after the somatic response conditioned by the same stimulus has been extinguished.[9] In his words, the organism remembers with its heart, but not with specific movements. "Thus the emotional basis for action remains after the external and superficial movements of adaptation have been lost. . . . The organism is being pounded by past emotional memories, which prepare it for an act no longer required."[9] In view of the effect of reserpine on conditioned cardiac and respiratory reflexes, it is possible that one of its clinical benefits depends on its ability to modify or abolish old conditioned visceral and viscerosomatic responses that have long since ceased to serve any adaptive purpose.

hippocampal seizures provides a means of assessing the effect of the deprivation of limbic function on behavior.

Without special tests or manipulations it is difficult to appraise the changes in an animal's behavior during hippocampal seizures. The results of experiments employing conditioning methods are summarized. It has been found that hippocampal seizures disrupt the performance of animals trained in conditioned escape behavior. It has also been demonstrated that such seizures may abolish or markedly alter conditioned cardiac and respiratory responses.

Reserpine is now widely used for the treatment of psychiatric disorders and hypertensive cardiovascular disease. A number of incidental observations are cited that suggest certain similarities between the behavior of a reserpine-treated cat and one subjected to a hippocampal seizure. This impression is reinforced by an experiment reported here where the administration of reserpine resulted in the abolition of conditioned cardiac and respiratory responses. Electroencephalographic and cerebral radioautographic studies are described that provide inferential evidence that a neural system involving the hippocampus and hypothalamus may be an important site of action of reserpine.

Some aspects of the relevance of the foregoing studies to behavioral problems are considered in the discussion.

REFERENCES

1. Broca, P.: Anatomie comparée des circonvolutions cérébrales: le grand lobe limbique et la scissure limbique dans la série des mammifères. Rev. anthrop., 1878, *1*, 385-498.
2. Creutzfeldt, O. D. and Meyer-Mickeleit, R. W.: Patterns of convulsive discharges of the hippocampus and their propagation. EEG clin. Neurophysiol., 1953, suppl. no. 3, 43.
3. Flanigan, S., Gabrieli, E. R., and MacLean, P. D.: Some applications of cerebral radioautography employing S^{35}-labeled l-methionine. (Submitted for publication)
4. Flynn, J. P. and MacLean, P. D.: Effects of hippocampal seizures on conditioned behavior. (Work in progress)
5. Fulton, J. F.: *Frontal lobotomy and affective behavior. A neurophysiological analysis.* New York, W. W. Norton and Company, Inc., 1951, 159 pp.
6. Gantt, W. H.: Principles of nervous breakdown—schizokinesis and autokinesis. Ann. N. Y. Acad. Sc., 1953, *56*, 143-163.
7. Green, J. D. and Arduini, A.: Rhinencephalic responses to afferent stimulation. XIX International Physiological Congress. Abstracts of communications, 1953, 409-410.
8. Green, J. D. and Arduini, A. A.: Hippocampal electrical activity in arousal. J. Neurophysiol., 1954, *17*, 533-557.
9. Jung, R. and Kornmuller, A. E.: Eine Methodik der Ableitung lokalisierter Potentialschwankungen aus subcorticalen Hirngebieten. Arch. Psychiat., 1938, *109*, 1-30.

10. Kaada, B. R.: Somato-motor autonomic and electrocorticographic responses to electrical stimulation of 'rhinencephalic' and other structures in primates, cat and dog. Acta physiol. scand., 1951 (Suppl. 83), *24*, 285 pp.

11. Kim, C. and MacLean, P. D.: Electroencephalographic study comparing effects of neuropharmacological agents on limbic and neocortical systems. (In preparation)

12. Liberson, W. T. and Akert, K.: Observations on electrical activity of the hippocampus, thalamus, striatum and cortex under resting conditions and during experimental seizure states in guinea pigs. EEG clin. Neurophysiol., 1953, *5*, 320.

13. Liberson, W. T. and Akert, K.: Hippocampal seizure states in guinea pig. EEG clin. Neurophysiol., 1955, *7*, 211–222.

14. MacLean, P. D.: Psychosomatic disease and the "visceral brain." Recent developments bearing on the Papez theory of emotion. Psychosom. Med., 1949, *11*, 338–353.

15. MacLean, P. D.: Some psychiatric implications of physiological studies on frontotemporal portion of limbic system (visceral brain). EEG clin. Neurophysiol., 1952, *4*, 407–418.

16. MacLean, P. D.: The limbic system and its hippocampal formation. Studies in animals and their possible application to man. J. Neurosurg., 1954, *11*, 29–44.

17. MacLean, P. D.: Hippocampal studies: their possible bearing on neuropsychiatry. Arch. Neurol. Psychiat. (Chicago), 1955, *74*, 219–220.

18. MacLean, P. D.: The limbic system ("visceral brain") in relation to central gray and reticulum of the brain stem. Psychosom. Med., 1955, *17*, 355–366.

19. MacLean, P. D., Horwitz, N. H., and Robinson, F.: Olfactory-like responses in pyriform area to non-olfactory stimulation. Yale J. Biol. Med., 1952, *25*, 159–172.

20. Papez, J. W.: A proposed mechanism of emotion. Arch. Neurol. Psychiat. (Chicago), 1937, *38*, 725–743.

21. Pribram, K. H.: Concerning three rhinencephalic systems. EEG clin. Neurophysiol., 1954, *6*, 708–709.

22. Scoville, W. B.: The limbic lobe in man. J. Neurosurg., 1954, *11*, 64–66.

23. Stevens, J. R. and MacLean, P. D.: Effects of hippocampal seizures on conditioned escape behavior. (In preparation)

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THE LOCALIZATION OF HYPOTHALAMIC STRUCTURES IN THE RAT INFLUENCING WATER CONSUMPTION‡

Hyperphagia and obesity occur following bilateral destruction of the ventromedial region of the hypothalamus.[1,2,3,10] On the other hand, bilateral destruction in the lateral area leads to anorexia and death.[1,2] In the rat, the ventromedial lesions also produce a reduced water/food intake ratio, a delayed excretion of a water load, increased tubular reabsorption of water,[7] and a small but significant increase in serum sodium.[15] These signs were considered "reflections of a chronic state of relative dehydration. The low water/food intake ratio implies a deficit in the neural mechanism responsible for thirst and its alleviation."[10] This "hypothalamic hypodipsia" can appear following such lesions, regardless of the presence or absence of hyperphagia and the development of obesity[10,15]; it, like hypothalamic hyperphagia and diabetes insipidus, is not fatal to the animal. That the hypothalamus influences thirst has been confirmed by the induction of thirst in goats upon injection of hypertonic saline into the medial portion of the hypothalamus.[8]

The purpose of the present study was to locate more precisely that area of the hypothalamus the destruction of which produces chronic "hypodipsia."

METHODS

Female rats of the Sprague-Dawley strain with an initial weight of 200–250 gm. were used throughout the investigation. All animals were housed in individual cages at an environmental temperature of 25.5 ± 1° C. and were fed a synthetic, high carbohydrate diet containing the necessary salt and vitamin requirements for the rat. This diet yielded 4.18 kcal/gm.; approximately 70% of the calories were provided by sucrose, 10% by fat, and 20% by casein. Food and water consumption as well as body weight of all rats was recorded to the nearest gram at two-day intervals, beginning five days after the operation.

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Hypothalamic lesions were placed with the aid of a Horsley-Clarke stereotaxic instrument as adapted for the rat by Clark.[6] For the operation each rat was anesthetized with Evipal (140 mgm./kg. body weight) intraperitoneally. The coordinates employed in placing the lesions (Fig. 1) were those appropriate for our stereotaxic instrument; they are not universal, and may vary from one instrument to another. These coordinates along with their expected hypothalamic locations are seen in Table 1. In Figure 1, the mid-sagittal plane is represented by the line O. The lines labelled R_1, R_2, and L_1, L_2, represent distances 1 and 2 mm. on either side of the mid-sagittal plane. Positions anterior to the zero frontal plane, which runs through the external auditory meatus, are represented by the lines A_4, A_5, A_6, A_7, and A_8. All lesions were placed 1 mm. above the base of the brain using a current of 1.5 ma. flowing for 15 seconds.

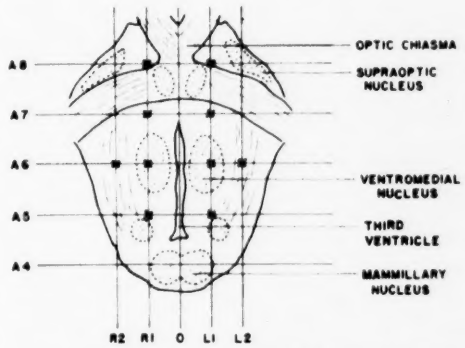

FIG. 1. Diagram of the hypothalamus of the rat (ventral view) showing the Horsley-Clarke coordinates employed. The line labelled O represents the mid-sagittal plane of the brain. Lines labelled R_1, R_2 and L_1, L_2 represent planes 1 mm. on either side of the mid-sagittal plane. Lines labelled A_4, A_5, A_6, A_7, and A_8 represent planes anterior to the zero frontal plane which runs through the external auditory meatus. The crosses indicate positions of the lesions.

The true location, symmetry, and extent of these lesions were later determined histologically. The rats were sacrificed under anesthesia by viviperfusion with saline followed by 10% formalin. The brain was removed, the hypothalamic area dissected free, frozen (CO_2), and sectioned at 20 microns. The sections were stained with cresyl violet, cleared in xylol, and prepared for microscopic observation.

RESULTS

A. Lesions producing the greatest degree of obesity. From the reports of previous investigators[1, 3, 11] one would expect to find the greatest degree of "hyperphagia" and obesity in rats with lesions in the immediate region of the ventromedial nuclei. This was confirmed in the present study (Table 2). The group A_6, R_1, L_1 ate 24.2 ± 2.2 gm. of food/day and gained 4.8 gm. body weight/day, while the controls ate 13.2 ± 0.2 gm./day and gained 0.8 gm. body weight/day. Plate Ia is a photomicrograph of the hypothalamus of rat A_6, R_1, L_1, 217 showing the extent of damage. In this rat, both lesions which were roughly 1 mm. in diameter were situated in the ventromedial nuclei, but destruction had encompassed a sphere roughly 2 mm. in diameter.

The group of rats with lesions 1 mm. more rostral (A_7, R_1, L_1) showed slightly less hyperphagia. The relatively large standard error of the mean food consumption (Table 2) indicates a wide variation among the animals in this group and this was also true of the location of the lesions. Those rats

TABLE 1. EXPECTED LOCATION OF HYPOTHALAMIC LESIONS

Coordinates	*Location*
A_8, R_1, L_1	In the frontal plane of the optic chiasma medial to the supraoptic nuclei.
A_7, R_1, L_1	In the frontal plane of the anterior hypothalamic areas, just lateral and ventral to the filiform nuclei.
A_6, R_1, L_1	In or around the ventromedial nuclei of the median eminence.
A_6, R_2, L_2	In the lateral hypothalamic areas at the same frontal plane as the ventromedial nuclei.
A_5, R_1, L_1	In the frontal plane of the ventral premammillary nuclei.

TABLE 2. FOOD AND WATER INTAKES OF RATS WITH HYPOTHALAMIC LESIONS AND FED A HIGH CARBOHYDRATE DIET

Location of lesions†	*No.*	*Duration days*	*Food gm./rat/day*	*Water cc./rat/day*	*Water/Food cc./gm./rat/day*
A_8, R_1, L_1	5	16	23.3 ± 1.7*	24.6 ± 2.8	1.06 ± 0.13
A_6, R_1, L_1	9	14	24.2 ± 2.2	27.5 ± 6.1	1.12 ± 0.22
A_6, R_2, L_2	5	16	16.4 ± 2.1	15.8 ± 1.1	1.00 ± 0.11
A_7, R_1, L_1	6	16	24.1 ± 3.2	30.7 ± 5.0	1.47 ± 0.42
A_5, R_1, L_1	2	16	18.3 ± 1.1	23.5 ± 2.7	1.30 ± 0.20
Control	11	16	13.2 ± 0.2	26.1 ± 2.6	1.97 ± 0.20

* S.E.M.
† Horsley-Clarke coordinates.
Significance of difference from control values:
Solid underlining — $P < .01$.
Dotted underlining — $P < .05$.

with high food consumptions had lesions impinging upon the anterior portions of the ventromedial nuclei, while those with low food consumptions had elongated lesions in the coronal plane of the filiform nuclei. A photomicrograph of a hypothalamus from this latter sub-group is shown in Plate Ib.

Rats with lesions placed in the regions of the premammillary nuclei (A_5, R_1, L_1) demonstrated less hyperphagia and obesity than the group A_8, R_1, L_1. Plate Ic is a photomicrograph showing the lesions present in

rat A_5, R_1, L_1, 205. They are very similar to those of rat 217 (Plate Ia) in size and symmetry but are situated in the coronal plane of the premammillary nuclei.

Four of the six rats receiving lesions in the preoptic regions (A_5, R_1, L_1) died within a few days after the operation. The remaining two exhibited a slight hyperphagia and weight gain. Plate Id illustrates the lesions present

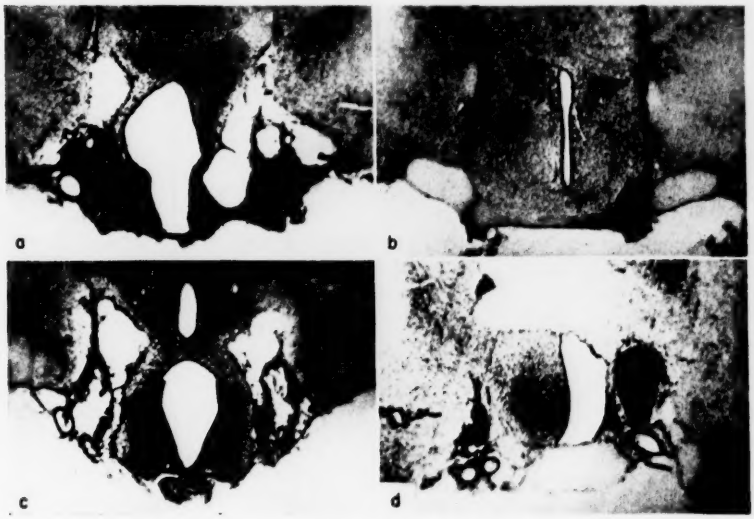

PLATE I. Photomicrographs of sections from the hypothalamus of
(a) Rat A_6, R_1, L_1, 217
(b) Rat A_5, R_1, L_1, 256
(c) Rat A_6, R_1, L_1, 205
(d) Rat A_5, R_1, L_1, 259
The lesions appear as black masses in the photomicrographs. Cresyl violet x38.

in one of the survivors. Both survivors had asymmetrical lesions, the right one more lateral and smaller than the left. The four fatalities in this group had symmetrical lesions in the preoptic nuclei.

The group of rats with lesions in the lateral hypothalamic areas (Table 2, A_6, R_2, L_2) showed no significant increase in food consumption and only a slight weight gain. This is in contradistinction to the anorexia and weight loss reported by Anand and Brobeck[1,2] and which has been observed previously in this laboratory. For some unknown reason the present lesions (Plates IIa, b, c) were smaller than those placed in any of the other rats and those reported by Anand and Brobeck.

B. *Lesions producing the greatest degree of hypodipsia.* All of the hypothalamic lesions in the present study produced a lowered water/food ratio (Table 2). The ratios were significantly lower than those of the controls only for the groups with lesions in the middle and caudal hypothalamus. The greatest decrease in the ratio appeared in those rats which did not demonstrate hyperphagia. In the other four groups the low ratio was the result of an elevated food consumption with little change in water intake following the operation.

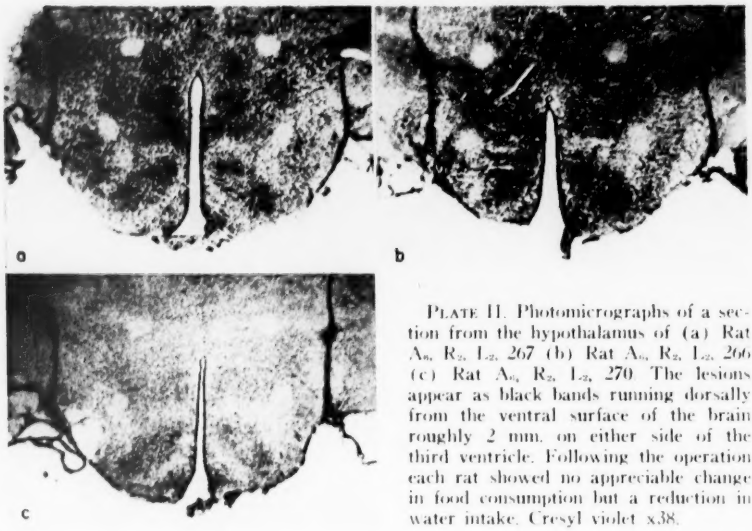

PLATE II. Photomicrographs of a section from the hypothalamus of (a) Rat A_8, R_2, L_2, *267* (b) Rat A_6, R_2, L_2, *266* (c) Rat A_6, R_2, L_2, *270*. The lesions appear as black bands running dorsally from the ventral surface of the brain roughly 2 mm. on either side of the third ventricle. Following the operation each rat showed no appreciable change in food consumption but a reduction in water intake. Cresyl violet x38.

The rats with lesions in the lateral hypothalamic areas (A_6, R_2, L_2), however, showed only a slight increase in food consumption but a selective and absolute decrease in water intake (difference from controls $P < 0.05$). These lesions, situated at the same frontal plane as the ventromedial nuclei, were consistently small and elongated, destroying a narrow band of tissue through the lateral hypothalamic areas. Plate IIa is a photomicrograph of the lesions present in rat A_6, R_2, L_2, *267*. Here the lesions are represented by the dark-staining bands running from the ventral surface of the brain dorsally through the lateral hypothalamic areas. The ventromedial nuclei, dorsomedial nuclei, the column of the fornix, and mammillothalamic tracts all remain intact. Although this animal's food consumption (15 gm./day) was approximately the same as that of the controls, its water intake (13.5

gm./day) was only about half that of the controls (Table 2). The lesions present in rats A_6, R_2, L_2, 266 and 270 (Plates IIb and IIc) were very similar to those of rat 267. Both of these rats showed an elevated food intake, 20.3 gm. and 20.0 gm./day respectively. Nevertheless, their water intake (16.6 and 17.3 cc./day) was decidedly lower than that of the controls (Table 2). It appears, then, that small lesions in the lateral hypothalamic areas produce little change in food consumption but a definite reduction in water consumption.

DISCUSSION

It is now well accepted that experimental hypothalamic obesity is largely the result of a dramatic increase in food intake, "hypothalamic hyperphagia."[1] The exact mechanism of the hyperphagia still remains obscure. Anand and Brobeck[1,2] held that destruction of the ventromedial nuclei released a "feeding center" situated in the lateral hypothalamic areas from inhibition—hyperphagia resulted. Lesions placed in this lateral feeding center resulted in anorexia and death.

In 1949, Stevenson demonstrated that rats subjected to hypothalamic lesions showed not only hyperphagia but also "hypodipsia"; his rats did not drink as much water per gram of food eaten as did the controls. In the present study we have attempted to find an area or areas within the hypothalamus which may be responsible for the hypodipsia. We have again found that all of the rats which showed hyperphagia, ranging from moderate to extreme, also demonstrated a relative hypodipsia. In most, this was the result of an elevated food intake with no change in water consumption.

On first glance this would seem to be evidence that such lesions produced no abnormality in water metabolism. However, when the composition of the diet and other conditions are kept constant, the ad libitum water intake of the normal rat varies more or less directly with the amount of food eaten whether this be varied by increasing the food requirement or by restricting its supply. The hypothalamic animals failed to show this correlation of water with food intake. Indeed, their lower water/food intake ratio persists when they are pair-fed with their controls or when the supply of water is restricted to 10 cc. per day. Hypothalamic "hypodipsic" rats also fail to increase their water intake when transferred from an environment of 22° C. to one at 35° C.[13] The results of these studies suggest an abnormal situation where the fine adjustment of water metabolism has been in some way impaired by the hypothalamic lesions. We have not been able to produce complete absence of voluntary water drinking.

Although the regulation of renal water excretion has been clearly associated with the supraoptic nuclei in the anterior hypothalamus,[4,15] the

regulation of water intake has not been as accurately localized. In the present study, the greatest reduction in the water/food intake ratio occurred in those rats with lesions in the lateral aspects of the lateral hypothalamic areas (Table 2, A_6, R_2, L_2).

Unlike the hyperphagic groups, those animals maintained a relatively normal food intake but reduced their water consumption. Here, then, is an area within the hypothalamus, the destruction of which has produced little obvious change in energy metabolism but changes in the animal's water economy. It would appear from these studies that a "thirst center," postulated by Stevenson,[11] may be located in or near the region of the lateral "feeding center." Because of the proximity of the ventromedial nucleus it is possible that obesity-producing lesions may impair the normal function of this lateral "thirst center."

The exact nature of the stimulus to this area and the mechanism by which it responds to produce a physiological effect require further investigation. In recent years evidence has been presented in favor of an osmotic stimulus. Andersson[1] has produced immediate polydipsia in the conscious goat by intrahypothalamic injections of hypertonic saline. Larsson[12] reports a transient hyperphagia following intrahypothalamic injections of hypertonic saline in the goat. There is little doubt that a close relation between water regulation and energy metabolism exists. It seems possible that an integrated regulation of both these essential functions is situated in the same area within the hypothalamus.

SUMMARY

With the use of the Horsley-Clarke stereotaxic instrument, electrolytic lesions have been placed at various bilateral loci in the hypothalamus of the rat from the preoptic region to the premammillary nuclei. Variations in food and water intake and body-weight gain were correlated with the histological localization of the lesions. The results were as follows:

1. The greatest degree of hyperphagia and obesity was obtained in those rats with lesions in or around the region of the ventromedial nuclei.

2. The water/food intake ratios were lower than those of the controls in all operated rats, but significantly so only for those rats with lesions located in the middle and caudal hypothalamus.

3. Rats with lesions which produced the greatest degree of hyperphagia and obesity also demonstrated "hypodipsia." In these cases the low water/food intake ratio was due to a dramatic increase in food consumption without any significant increase in water intake.

4. Rats with lesions in the lateral hypothalamic areas showed no significant increase in food intake but a reduction in water intake. The

hypothalamic area responsible for this "hypodipsia" thus appears to be situated predominantly in the lateral hypothalamic areas in the same frontal plane as the ventromedial nuclei. This hypothalamic area which has been previously shown to be important in the regulation of food intake—the "feeding center"—is apparently also important in the normal regulation of water intake.

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REFERENCES

1. Anand, B. K. and Brobeck, J. R.: Hypothalamic control of food intake in rats and cats. Yale J. Biol. Med., 1951, *24*, 123.
2. Anand, B. K. and Brobeck, J. R.: Localization of a "feeding center" in the hypothalamus of the rat. Proc. Soc. exp. Biol. (N.Y.), 1951, *77*, 323.
3. Andersson, Bengt: Polydipsia caused by intrahypothalamic injections of hypertonic NaCl solution. Experientia (Basel), 1952, *8*, 157.
4. Brobeck, J. R.: Mechanism of the development of obesity in animals with hypothalamic lesions. Physiol. Rev., 1946, *26*, 541.
5. Brobeck, J. R., Tepperman, Jay, and Long, C. N. H.: Experimental hypothalamic hyperphagia in the albino rat. Yale J. Biol. Med., 1943, *15*, 831.
6. Clark, George: The use of the Horsley-Clarke instrument on the rat. Science, 1939, *90*, 92.
7. Fisher, Charles, Ingram, W. R., and Ranson, S. W.: *Diabetes insipidus and the neuro-hormonal control of water balance: a contribution to the structure and function of the hypothalamico-hypophyseal system.* Ann Arbor, Michigan, Edwards Bros., 1938.
8. Hetherington, Albert: The relation of various hypothalamic lesions to adiposity and other phenomena in the rat. Amer. J. Physiol., 1941, *133*, 326.
9. Hetherington, A. W.: The production of hypothalamic obesity in rats already displaying chronic hypopituitarism. Amer. J. Physiol., 1943, *140*, 89.
10. Hetherington, A. W.: Non-production of hypothalamic obesity in the rat by lesions rostral or dorsal to the ventromedial hypothalamic nuclei. J. comp. Neurol., 1944, *80*, 33.
11. Hetherington, A. W. and Ranson, S. W.: The relation of various hypothalamic lesions to adiposity in the rat. J. comp. Neurol., 1942, *76*, 475.
12. Larsson, Stig: On the hypothalamic organisation of the nervous mechanism regulating food intake. Acta physiol. scand., 1954, *32*, suppl. 115.
13. Montemurro, D. G. and Stevenson, J. A. F.: Observations to be published.
14. Stevenson, J. A. F.: Effects of hypothalamic lesions on water and energy metabolism in the rat. Recent Prog. Hormone Res., 1949, *4*, 363.
15. Stevenson, J. A. F., Welt, L. G., and Orloff, Jack: Abnormalities of water and electrolyte metabolism in rats with hypothalamic lesions. Amer. J. Physiol., 1950, *161*, 35.
16. Verney, E. B.: The antidiuretic hormone and the factors which determine its release. Proc. roy. Soc. B., 1947, *135*, 25.

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THE FIELD FUNCTION ON THE BODY SURFACE DURING MOMENTS IN THE U WAVE IN NORMAL SUBJECTS AND IN PATIENTS WITH CARDIAC PATHOLOGY‡

Attention to the U wave is practically nonexistent among clinical electrocardiographers. Nevertheless, this wave exists, is most frequently found in the precordial leads and less often in the limb leads. Characteristically, when the U wave is present, its direction is generally the same as that of the T wave which it follows. Its greatest amplitude seems to be found in V2-V4 or 5, and then it declines and disappears in V6 and V7. In rare instances an inverted U in the precordial leads may be the only evidence in the electrocardiogram of the existence of heart disease. There are times when it falls on the downstroke of T, while at other times it appears in a diphasic terminal portion of T. In practically all observations thus far made it was found in a fixed time relationship with Q.*

It cannot be assumed that because U is in a fixed time relationship with Q, the QU interval is a measure of the refractory period of the ventricle. In the intact dog heart, the basal fibers of the left ventricle were found to emerge from the refractory period last, and this moment corresponded with the end of T in the precordial electrocardiogram. The refractory period was never found to extend to where U would terminate.[1] We must therefore recognize that U is independent of the refractory period, and this makes it necessary to seek for its explanation in electrical events in excitable tissue that occur after the refractory period. That such a phenomenon exists can be seen in the work of Erlanger and Gasser, who have shown both negative and positive after-potentials long after the period of excitation accompanying the propagation of the nerve impulse. Such after-potentials seem to be associated with various phases of recovery and are profoundly influenced by metabolic mechanisms affecting recovery.

Many of the speculations offered to explain the origin of the U wave invoke an extracardiac as well as cardiac origin. In general most observers

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now believe that it arises from electrical activity in the ventricles and is in some way related to the recovery of the ventricle from excitation even though it occurs after the refractory period is completed. If it is an electrical event arising in the heart muscle as a result of excitation, then an electric field should be present during its inscription. If we knew what the characteristics of this field were, perhaps some of the objective findings regarding the U wave mentioned above would find a satisfactory explanation. In this communication the potential distribution during moments in the U wave has been established in normal subjects and those with cardiac pathology, and it will be seen that the reason for the distribution and character of this wave in the different leads begins to become clear.

METHOD

The method for obtaining the potential field at any given instant in the cardiac cycle and for drawing equipotential lines has already been described in detail.[1] Two channels of information were recorded simultaneously. One channel served as the time reference electrocardiogram, the other as the recording channel made up of the potential at the exploring electrode paired with the Wilson central terminal as a fixed electrode. Thus, for any moment in time the data were analyzed for the instantaneous algebraic value of potential of the exploring electrode with respect to the central terminal. It is important to recognize that with potential values as low as are obtained during the U wave they may almost be considered to have absolute significance since with such low values at the limbs the potential at the central terminal is probably zero. It will be observed from the diagrams that it was possible with the aid of a binocular microscope and magnification of 30 x to measure potential values almost exactly to within 0.1 of a mv. However, most of the number values were distinctly larger than 0.1 mv. and this permitted the establishment of the geometric properties of the equipotential lines at all values without difficulty.

RESULTS

In the first set of data (Figs. 1 and 2) the instantaneous equipotential distribution is shown for two normal male subjects. The instant in Figure 1 was that moment in time defined as 460 msec. after the onset of R in L3. In this subject the QT interval measured 380 msec. The instant in Figure 2 is 480 msec. after the onset of R in the time reference electrocardiogram. In this record the QT interval was 360 msec. In both diagrams the moment corresponded with the summit of U. It may be seen that only the positive field is described. The negative values at other points on the chest were less than 0.1 mv. and therefore are not charted; however, the region could be vaguely recognized as occupying the right shoulder, the right limb attachment, and right axilla.

In Diagrams 3 and 4 may be seen the potential field at two moments during the U wave 570 and 624 msec. after the onset of R in the time reference electrocardiogram of a patient with left ventricular hypertrophy and left bundle branch block. The QT duration was 507 msec. In Diagram 3 it is possible to distinguish both a positive and a negative region of the

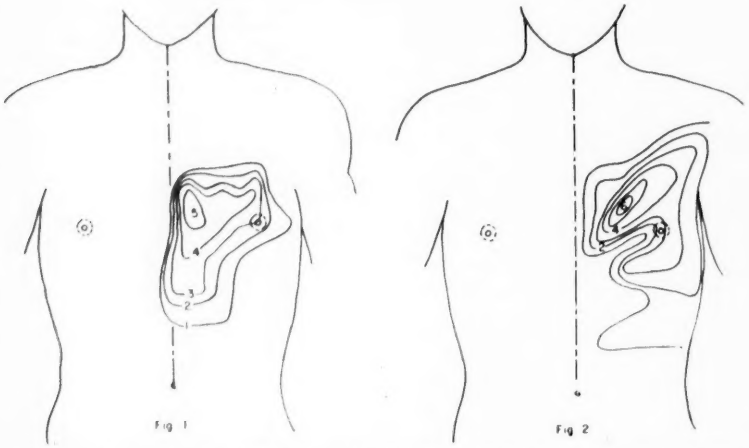

FIG. 1. Equipotential distribution during U in a normal male 18 years old. This diagram is the same as one on upstroke and downstroke of U, only the number values varied.

FIG. 2. Equipotential distribution during U in a normal male 28 years old. This diagram also is the same as one obtained on upstroke and downstroke of U, only the number values varied.

distribution. Again, the positive region occupies the left precordium, but the negative region is now in the left axilla. Contrast this with the normals where the negative region probably occupied the right axilla and shoulder. These diagrams are examples of many potential fields plotted during various moments in the U wave, on its ascending slope and on the downswing from the summit as well as at the summit. The striking feature characterizing all of them is the identity of the geometric form of potential distribution at all moments during the U wave, only the number values of the lines varying in each diagram. Diagram 4 is a field plotted 54 msec. later in the same subject and shows the positive region not to have changed in position or in its geometric form, but the negative region has waned and is no longer recognizable.

One general feature that characterizes the potential fields in all the diagrams is the marked asymmetry of the equipotential lines and their

striking irregularity. In this feature they are altogether similar to other potential fields already described during the QRS and T complexes in normal subjects and those with cardiac pathology.[2,3,4]

DISCUSSION

The above data in a most striking manner reveal that an electrical disturbance occurs during the U wave, for we find at various moments

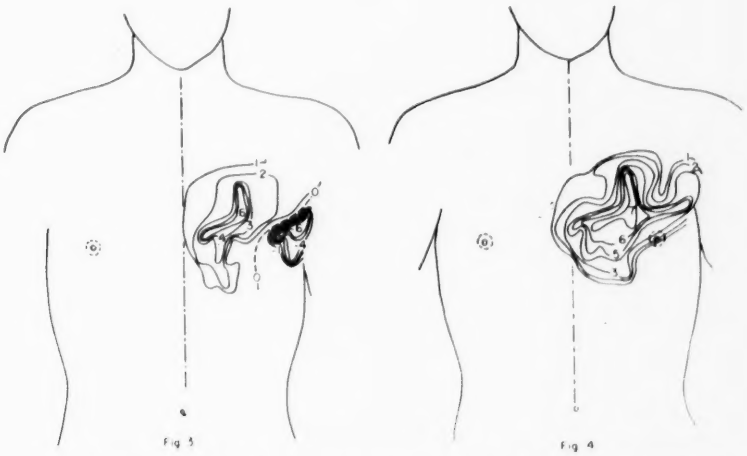

FIG. 3. FIG. 4.

FIG. 3. Equipotential distribution during upstroke of U in a subject with hypertensive cardiovascular disease with left bundle branch block, aged 66.

FIG. 4. Same subject as in Figure 3, but 54 msec. later. Description in text.

during T a two-pole distribution—that is, a region of positive and negative potential. Unfortunately, surface potential measurements cannot in principle necessarily and sufficiently elucidate the real source of the potential. The magnitude of the potential values, however, is such as to preclude their origin in the recoil of the aorta or the flow of blood through it. It is unlikely that the rapid inflow of blood in early diastole gives rise to an electrical disturbance sufficient to cause the U wave, for if this were so, then the U wave while varying in amplitude according to velocity and volume of inflow could not vary in sign. Accordingly, U would always remain negative in VR where it normally is, and positive in the precordium where it normally is. Diagram 3, however, shows a negative field in the left axilla instead of the right, and negative U waves have been encountered in the precordial leads in diseased hearts with and without T wave changes.[5] We are led to

the conclusion that the kinetics of diastolic inflow cannot explain the genesis of the U wave. It is also difficult to attribute the potential field during U to the distension of the ventricles by the inflow of blood during diastole, since the greatest distension occurs in presystole, while the strongest potential field occurs in earliest diastole. We are accordingly led to postulate that the current source is in the ventricles and represents a phase of the recovery process.

Support for this hypothesis may be derived from the following. The location of the positive distribution is directly over the heart suggesting that it arises there. As one travels from the precordium, the potential falls off rapidly so that the negative part of the distribution, especially in the normal subjects, becomes so attentuated as to be unrecognizable. The geometric form of the positive potential field is almost exactly like that during the ST segment and various moments in the T wave. This directs attention to the possibility that the recovery processes in the ventricles which are reflected in the formation of ST and T[2,3] are also at the basis of the U wave.

The problem arises whether U may be attributed to the late termination of the refractory period in some fibers that are late to recover, as, for example, those somewhere in the septum. Aside from the fact that no evidence has been adduced to support such a view, there are some observations against it. Our observations on the termination of the refractory period in various parts of the intact dog left ventricle have shown that the latest fibers to recover are not in the septum but in the left ventricular base. Their refractory period terminates at the end of T or shortly thereafter, but not as late as U. What is equally important, however, is that the positive potential distribution of T and U is almost identically located. The close similarity between the location and the geometric form of the U and T fields in the normal is equalled by the identity of their nonrotating properties. The potential function during U merely waxes and wanes in time just as had been shown to occur during T and this is strikingly different from that during the QRS where rapid rotation and shifting of the maxima in space occurs.[1,4]

The irregularity of the potential lines in all the diagrams supports the view that the source of the potential in the heart giving rise to the electric field is as complicated as is that which gives rise to the fields during the QRS, ST, and T. If the source were a simple dipole, the potential distribution on the body surface would be expected to be as already described for an intrathoracic bipole, namely, smooth regular lines.[5] The conclusion would appear to be warranted that all the heart fibers contribute to the field; because of the variation in time and duration of the "after-potential" in the

complex heart mass, the resulting potential field on the surface is complex also.

Some explanations for the electrocardiographic findings regarding U in the various leads now emerge. The low potential at the limbs makes a recording of U difficult in limb leads and explains its greatly reduced frequency in these leads. The highest potential values are found directly over the heart mass, represented by position V2-V5. It is in these leads that U is most prominent. Since the potential falls away towards the axilla, the U wave should flatten and disappear in these leads as it actually does. The potential fields in the normal subjects merely wax and wane in time without rotation. This accounts for the occurrence of a positive or a negative U in a lead but not a diphasic complex. Finally, the locations of the positive and negative regions occupy the same areas as they do during the ST segment and T wave. This explains why the U in general is positive or negative as the T is positive or negative. There still remains to be explained the rare case in which the precordial T waves are positive while the U wave is negative. Further charting of such fields should throw light on this strange phenomenon. It is probable, however, that what has occurred is a shift of the negative region normally occupying the left axilla in some cardiac subjects towards and over the left precordium.

Not enough is known to permit speculation as to whether the factors responsible for the electric field during T are similar to those during U. It might be suggested, however, since the precordium is positive, that during the after-potential the recovery of the heart underlying this region occurs sooner or faster than in other regions of the heart, thus rendering this area positive and the overlying surface positive.

The nature of the post-refractory processes that may be involved in the genesis of the U wave can only remain in the realm of speculation at present. Electrical activity at this period in the recovery process would exist especially if a supernormal period were present. That this can occur is attested by experiments on nerve, skeletal muscle, and the dog and chimpanzee ventricle. The presence of ectopic beats mostly occurring during this period directs attention to the existence of a supernormal period in many such instances, since ectopic beats and supernormality are believed to be dependent one upon the other.[7]

Nevertheless, the occurrence of a U wave in the normal male makes it unlikely that its genesis in the normal can be related to the existence of a supernormal period. In the intact dog ventricle supernormal periods are not encountered. If the normal human heart is not different metabolically from the normal dog heart, then the normal human heart also probably does not possess a supernormal period. The normal human subject, however, does

have a U wave in the electrocardiogram and exhibits a potential field on the body surface during moments in the U. It must be considered, therefore, that other electrical processes besides the supernormal period can participate in the genesis of the U wave.

SUMMARY

1. An electric field exists during the U wave which waxes and wanes.

2. Its characteristics are similar to the field during the T wave which it follows.

3. The complexity of the equipotential lines points to a complex electrical source in the heart.

4. Clinical types of U waves are deducible from the potential distribution.

5. The nature and location of the distributions makes it unlikely that the U can be explained by electric forces generated by rapid inflow in early diastole.

6. The position of U in the cardiac cycle precludes its origin in potentials caused by cardiac distension.

REFERENCES

1. Mauro, A., Nahum, L. H., and Sikand, R. S.: Instantaneous equipotential distribution on the thoracic surface of human subjects with cardiac pathology. J. appl. Physiol., 1953, *5*, 698-704.

2. Nahum, L. H. and Hoff, H. E.: The interpretation of the U wave of the electrocardiogram. Amer. Heart. J., 1939, *17*, 585-598.

3. Nahum, L. H., Mauro, A., Chernoff, H. M., and Sikand, R. S.: Instantaneous equipotential distribution on surface of the human body for various instants in the cardiac cycle. J. appl. Physiol., 1951, *3*, 454-464.

4. Nahum, L. H., Mauro, A., Levine, H., and Abrahams, D. G.: Potential field during the ST segment. J. appl. Physiol., 1953, *5*, 693-697.

5. Powsner, E. R., Nahum, L. H., and Mauro, A.: Body surface potential distribution of an intrathoracic bipole as related to tissue conductivity in electrocardiography. Amer. J. Physiol., 1954, *177*, 467.

6. Sikand, R. S., Mauro, A., and Nahum, L. H.: Instantaneous distribution of electrocardiographic potential on the body surface of the normal man during the T interval. J. app. Physiol., 1952, *4*, 916-919.

7. Sikand, R. S., Nahum, L. H., Levine, H., and Geller, H.: Ventricular excitability in the intact dog heart. Yale J. Biol. Med., 1952, *24*, 366-380.

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SOME HIGH LEVEL SYMPTOMS IN ONE HUNDRED OPERATED TUMORS AFFECTING THE MESO-DIENCEPHALIC REGION

More than twenty-five years ago John Fulton was interested in the emotional disturbances following experimental lesions of the base of the brain (studies with Ingram in 1929), and in the symptoms produced by tumors of the third ventricle (paper from Cushing Clinic in collaboration with Percival Bailey, also in 1929).

From our own neurosurgical material of over one thousand brain tumors and expansive intracranial lesions, operated upon in Madrid during the last nine years, we have collected the first hundred examples of tumors localized near the meso-diencephalic area, third ventricle, and brain stem.

It is hardly necessary to insist on the well-known fact that tumor material is not very adequate for the study of the symptomatology of any cerebral region. The increase of intracranial pressure, the hydrocephalic dilatation of the ventricles, the edema of the nervous tissue, etc., represent variable factors that make very difficult the evaluation of our results. Besides, we find in many patients a confusing mixture of positive and negative symptoms that defy any careful physiological evaluation. The signs of irritation of one structure are frequently mixed with those expressing the liberation of lower levels and with others due to the diminution or absence of function. The extreme variability of similar clinical lesions is also well known and it is necessary, of course, to consider in addition to the localization and extension of the lesion the rate of development and growth of the tumor.

The cases studied from our material can be divided in the following groups:

56 predominantly "extrinsic" tumors	Pituitary adenomas	20
	Craniopharyngiomas	19
	Basal meningiomas	11
	Epidermoids	3
	Gliomas of the optic chiasm	3
44 predominantly "intrinsic" tumors	Tumors of the third ventricle	19
	Tumors of the pineal region and posterior part of the third ventricle	17
	Tumors of the brain stem	8

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In the revision of the clinical notes of these hundred cases we have found a great number of high level symptoms that can be separated in two main groups: preoperative and postoperative. We have excluded completely in this revision the epileptic phenomena.

The symptoms during operation on the diencephalic region were observed in only a few cases since we usually operate on our patients under general anesthesia. In five patients, however, under local anesthesia, we recorded periods of confusion, disorientation, agitation, or somnolence during the manipulation of tumors in the vicinity of the hypothalamus, and while approaching the third ventricle through the lateral ventricle or aftersection of the corpus callosum.

The obvious preoperative symptoms recorded in the clinical histories and their frequency can be grouped in the following way:

Mental changes, loss of memory, deterioration, etc.	12
Indifference and apathy	8
Somnolence	6
Emotional disturbances, depression	6
Disorientation, confusion, hallucinosis	5
Excitation, irritability, aggression	4
"Aquinesia"	2
Fatal coma	2

This great variety of clinical, high level symptoms in the patients suffering from tumors in the proximity of the meso-diencephalic region is even more rich during the postoperative period as might be expected because of the surgical trauma. The list of these postoperative symptoms runs as follows:

Excitation, agitation, disorientation, negativism	22
Somnolence and stupor	16
Confusion and hallucinosis	12
Indifference and apathy	7
"Aquinesia" and mutism	5
Emotional disturbances	5
Erotism and polyphagia	3
Moria	2
Reversible comas	2
Fatal comas	30

The study of the relative frequency of the high level symptoms in relation to the pathological type of tumor gave the following results:

		56 predominantly "extrinsic" tumors		44 predominantly "intrinsic" tumors	
Preoperative symptoms	Pituitary adenomas	0	Third ventricle	7
	Craniopharyngiomas	6	Pineal region	5
	Basal meningiomas	5	Brain stem	4
Postoperative symptoms	Pituitary adenomas	7	Third ventricle	5
	Craniopharyngiomas	4	Pineal region	3
	Basal meningiomas	5	Brain stem	3
	Fatal comas	17	Fatal comas	13

It seems that the preoperative high level symptoms are more frequent in the "intrinsic" tumors of the third ventricle and in the craniopharyngiomas and basal meningiomas compressing this region. Although the increase of intracranial pressure and the accompanying hydrocephalus may play a rôle in the development of these symptoms, the lesion of the region around the third ventricle as such appears to have some significance.

In the postoperative group of symptoms the removal of pituitary adenomas may be followed by very interesting syndromes. We have observed states of confusion, puerility, disorientation, amnesia, lack of attention, and abnormal behavior. In one of these cases with a late recurrence of the adenoma the autopsy disclosed only a moderate compression of the diencephalic region, from the optic chiasm to the mammillary bodies, that seemed to be responsible for the great mental changes. In two other cases of pituitary adenomas the patients showed, during several weeks following the operation, very marked psychic disturbances with confusion, disorientation, amnesia, lack of attention, and the continuous performance of organized acts, like playing cards, drinking, smoking, erotic excitation, etc. These curious clinical pictures have a certain similarity to other meso-diencephalic disturbances, like the Korsakoff syndrome with disorientation, amnesia, and confabulation.

In the predominantly "intrinsic" tumors of the third ventricle the frequency of fatal postoperative coma is unfortunately very high (9 cases). In other patients we observed apathy, somnolence, "aquinetic" mutism of Cairns, or the opposite states of agitation and irritability. Some curious and rather complex clinical pictures of organized visual hallucinosis together with different auditory sensations have been occasionally observed after operations for craniopharyngiomas.

Although it is very difficult to draw any physiological conclusions from such rough clinical and operative material, there is no doubt that tumors

invading or compressing the meso-diencephalic region produce different changes and disturbances in the high level cerebral activity. These changes vary from mild or moderate alterations in the personality, attention, memory, orientation and emotional reactions to more severe disturbances expressed as confusional delirious states, agitation and irritability, "aquinetic" mutism, negativism, somnolence and stupor ending in fatal states of coma. The vital importance of the meso-diencephalic region of the human brain is thus obvious, since our patients showed all degrees of disturbances. In this field, as in many others of neurophysiology, the correlation of experimental and clinical observations has an extreme importance. In his extensive studies on the central nervous system John Fulton has always taught and followed this line of research; for myself, as a neurosurgeon, I am most grateful for his teaching.

REFERENCES

1. Fulton, J. F. and Ingraham, F. D.: Emotional disturbances following experimental lesions of the base of the brain (pre-chiasmal). J. Physiol. (Lond.), 1929, *67*, xxvii-xxviii; Amer. J. Physiol., 1929, *90*, 353.
2. Fulton, J. F. and Bailey, P.: Tumors in the region of the third ventricle: their diagnosis and relation to pathological sleep. J. nerv. ment. Dis., 1929, *69*, 1-25; 145-164; 261-277. Nueva contribución sobre los tumores del tercer ventrículo. Su asociación con el síndrome de Recklinghausen y con el edema de Quincke. Arch. argent. Neurol., 1930, *5*, 3-27.

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JOAN D'ALOS AND THE DOCTRINE OF THE CIRCULATION OF THE BLOOD

The publication in 1628 of Harvey's *Exercitatio Anatomica de Motu Cordis*, was ignored by most of the faculties in the medical schools. Its experimental approach disturbed a world subdued by dogmatic medicine, and very few men realized the importance of the upheaval that was taking place in man's thinking.

The Sorbonne was particularly conservative in this position, revealed by implacable scorn and stubborn opposition to the teaching of the new doctrine; the Spanish medical schools shared in the attack and their most prominent leaders, headed by Matías García, author of *Disputationes Anatomicae Ab Harveyo Suscitatoe Motu Cordis Arteriarum et Sanguinis* (in folio, 1648), and Andrés Piquer, the "Spanish Hypocrates" (1711-1772), turned Valencia, and later Madrid, into very active centers opposing the circulation thesis; Salamanaca, Alcalá, and other universities took the same stand. J. J. Izquierdo refers to this opposition in his excellent book, *Harvey, Iniciador del Método Experimental.*[a] Later, when the circulation of the blood was generally accepted, several Spanish historians claimed predecessors to Harvey.

The Medical School in Barcelona may be considered as an exception because of two remarkable men, Francesc Morelló and Joan d'Alós. Morelló is the author of *Medicinale Patrocinium in Sanguinis Circulationem* (1678), a brief book containing a good description and defense of the circulation thesis. Joan d'Alós i Serradora, son of Jaume and Joana, Protophysician of the Princedom of Catalunya and Earldoms of Rosselló and Cerdanya, is a very interesting figure, active in political and medical circles. Born on April 16, 1617, in Moia, a mountain village about fifty miles north of Barcelona, he married Maria Ferrer in the Cathedral of Barcelona on July 18, 1657. He was elected city alderman in 1666; later, was a captain in the army in the medical corps (1684), and representative in 1690. Catedrático (Professor) of Prima de Medicina since 1664, he taught anatomy, aphorisms, and pharmacy. Upon his death in Barcelona on March 15, 1695, he was buried in the cemetery of the St. Michael Parish.

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Three of his books, all three very remarkable, are available. Chronologically, the first is *Pharmacomedica Dissertatio de Vipereis Trochiscis* (Barcelona, 1664). This booklet, a quarto of 34 pages, is a valuable study of

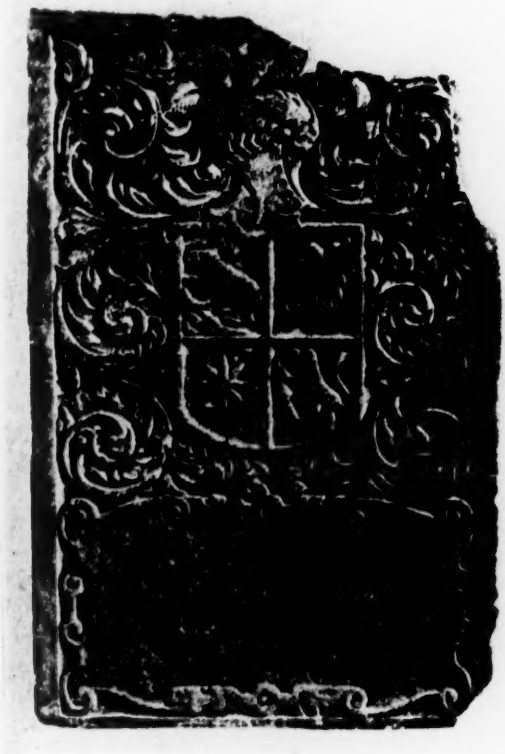

FIG. 1. Tombstone of the Alós family.

pharmacognosy and therapeutics, part of a controversy with Miquel Vilar, from Valencia. There is a copy in the Library of the Bishop's Palace in Barcelona—or at least there was a copy there in 1936 before the Civil War. Two years after publication the booklet was supplemented by *Pharmacopea Catalana Sive Antidotarium Restitutum et Reformatum* (Barcelona, 1666; 250 pages in folio). This was, as far as we know, the first intent of a mono-

graphic study of the local pharmacopea. The library of the Academy of Medicine in Barcelona has one copy of this book.

The third book, and by all means the most important, is *De Corde Hominis Disquisitio Physiologico-Anatomico*, published in Barcelona in 1694 by Joaquin Gascon. Antoni and Baltasar Ferrer are the printers. It is a beautiful volume of 247 pages, with a dedication to the Marques de Villena, with the customary review by Jaume Solá, also a professor at the Medical School, and the *Imprimatur* by R. P. Antoni Garrigó, countersigned by the Vicar General. The Medical School Library in Barcelona has six copies of this book and there is one copy each in the possession of the library of the distinguished Institut de Fisiologia, the Academy of Medicine (originally in the Library of the College of Surgery), and the Alós family. This does not pretend to be an exhaustive list; it includes only the copies found in Barcelona in a careful search for the preparation of a study on Joan d'Alós with Professor J. M. Bellido.

The text describes Harvey's doctrine in detail, with many valuable supplementary data and comments. A reading of the book does not seem to indicate that Alós checked Harvey's descriptions experimentally except, possibly, the most elementary ones such as the properties of venous circulation studied in human subjects. He appears very impressed with the book of the English anatomo-physiologist and insists on the value of a complete study and wide diffusion of Harvey's doctrine, regretting the qualifications of "incertain invention" given to obvious facts, a diaphanous allusion to Andrés Piquer. With clear vision not shared by most of his contemporaries, Alós affirms that "the doctrine of circulation, far from contradicting the natural curative methods, perfects and explains them." In Chapter XX "On the Circular Motion of the Blood," Alós summarizes the ideas exposed in the previous sections; the list of marginal headings for the various paragraphs evidences an approach completely divergent from contemporary Spanish books on similar subjects: "Harvey, Discoverer of Blood Circulation," "Meaning of Circulation," "Reply to Matías García," with a list of propositions by the Valencian physician—opponent of the circulation doctrine—and the corresponding refutation. Very interesting also is Chapter XXIV on blood transfusion, with a worthy description of methods, a discussion of the possibility of rejuvenation by blood from young animals, the prediction of therapeutic applications, and even a list of situations when the use of human blood might be feasible. This chapter and the following three, up to the end of the book, on the "Admirable Histories Showing Examples of the Heart Movements," "On the Admirable Constitution of the Arteries," and "On the Diverse and Notable Differences in Pulse" are the most original, enriched in some sections with new applications and observations.

Neither Chinchilla[1] nor García del Real[2] mentions Alós, although they discuss extensively the Spanish contribution to the knowledge of the circulation of blood, before or after Harvey. The catalogues of the New York Academy of Medicine and the New York Public Library do not include any of Alós's books, or any cross reference to his work.

Joan d'Alós was not an investigator, but he was fully aware of the signs of change and progress around him. He distrusted the traditional methods of disputations and formal reasoning, although using them in some sections of his books, and called impassionedly for the use of precise observations in exploring the human body and its functions. We see him at a distance as a scholar and leading physician, a member of a bourgeois family ennobled by the Archduke Charles of Austria during the War of the Spanish Succession. With an analytical mind, Alós devoted his leisure hours, out of an active practice, to public service in representative positions of government, and to the teaching of medicine. Although his book has been forgotten, it represents a valuable contribution to the studies on circulation.

REFERENCES

1. Chinchilla, Anastasio: *Anales históricos de la medicina en general y bibliográfico-bibliográficos de la Española en particular.* Valencia, Imprenta de Lopez y Compañia, 1841-1846. 4 vols.
2. García del Real, Eduardo: *Historia de la medicina en España.* Madrid, Editorial Reus, 1921.
3. Izquierdo, J. J.: *Harvey, iniciador del método experimental.* México, Ediciones Ciencia, 1936. xviii + 400 pp.

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OBSERVATIONS UPON CEREBELLAR CONVULSIVE ACTIVITY INDUCED BY STRYCHNINE‡§

For many years one of Professor John Fulton's major interests in neurophysiology has been the interpretation of cerebellar activity. His many contributions to the relationship of cerebellum and cerebrum have clarified the integration of the motor systems. The presentation of certain experimental findings concerning "convulsive" cerebellar activity would seem, then, to be appropriate on Professor Fulton's anniversary.

Some years ago in the course of studies on epileptic discharge, a group of Hopkins investigators[5] noticed an unusual type of high voltage, rapid cerebellar activity resulting from the intravenous injection of strychnine and other agents. It was thought at that time that this phenomenon had not previously been described, but one of us (G.F.P.) came upon an earlier reference in the Italian literature to this type of cerebellar reaction.[8] In the past five years this rhombencephalic convulsion has been analyzed by a number of investigators so that its characteristics may be briefly described as follows:

Following the intravenous injection of strychnine, nitrogen mustard, and dichloro-diphenyltrichloro-ethane (DDT) and, at times, after electrical stimulation of the cerebellum, regular, rhythmic waves of high amplitude (200-450 μv) at frequencies of 10-32 per second, lasting from minutes to several hours may be recorded from the cerebellar cortex, dentate nucleus, brainstem, and spinal cord.[1,2] These rhythmic discharges are not seen in the cerebral cortex,[2] but according to the study of Beaumont Johnson,[4] they implicate the cerebellum, brachium conjunctivum, tegmentum, reticular formation, and inferior olivary nucleus. The red nucleus and caudal portions of the thalamus and the fields of Forel are also involved, although the

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anterior part of the thalamus and basal ganglia are silent. That the cerebellar activity represents "the summated efferent discharge of the Purkinje cells" responding to afferent brainstem volleys has been suggested by Bremer and Bonnet,[1] who believe that the phenomenon is related to tetany of the afferent bulbo-spinal projection to the cerebellar cortex. They found that the anterior lobe of the cerebellum and the vermis had high voltage responses and the lateral lobes, low voltage spikes of inversed polarity which they believed were due to diffusion of the potentials from the vermis. It seems generally agreed now that these cerebellar discharges are, as originally described by Gualtierotti and Capraro,[3] due to bulbo-cerebellar circuits, and possibly spino-bulbo-cerebellar circuits.

The extent of cerebellar participation in these rhythmic discharges has occasioned some difference of opinion. In their early studies Markham, *et al.*,[7] thought that the phenomenon was present in both vermis and lateral cerebellar lobes, but Bremer and Gernandt[2] concluded that the activity of the lateral lobes was due to diffusion of the vermis potentials. In investigating this problem further we have noted several interesting findings which are presented in this paper.

METHOD

The present series of experiments has been performed on six cats. Under light ether anesthesia and local infiltration of the neck and scalp a tracheal cannula was inserted and the scalp incised. After pre- or transcollicular decerebration or uni- or bilateral subpial "sucker" resection of the occipital lobe the anterior lobe of the cerebellum was exposed by removal of the bony tentorium. Two animals were decerebrated during the course of the experiment. The posterior vermis and the paramedian lobule were exposed by a posterior craniectomy. The dura was opened wide and the cerebellar cortex covered with mineral oil. The ether was discontinued at least 1½ hours before the recording started.

The electrical activity was recorded with ball-tipped silver wire electrodes (0.6 mm. in diameter), resting upon the pial surface. In bipolar recording the interelectrode distance ranged from 1.5 to 2 mm. For monopolar recording the "indifferent" lead was clipped either to the temporal muscle or to the head holder. The activity was recorded with a Grass electroencephalograph, having a time constant of 0.1 second and a high range filter reducing the voltage 50% at 70 cps.

Just before the injection of strychnine, the animal was immobilized (succinyl-choline chloride, 30-40 mg. intravenously) and artificially ventilated. Strychnine phosphate—in dosage of 2.5 mg. in 2.5 % of aqueous solution—was injected through the saphenous vein. Usually one injection was sufficient to induce "convulsive" cerebellar activity lasting for the entire experiment, but occasionally a second injection was given at least two hours after the first if the synchronized activity had completely disappeared and could not be re-induced by auditory or somatic stimulation.

RESULTS

This study has confirmed the general characteristics of cerebellar "convulsive" activity following the intravenous injection of strychnine. No further description will be presented of these findings which are well described by Gualterotti and Capraro,[8] Markham, *et al.*,[3] and others.[1, 9, 10]

Extent of cerebellar discharge. The topical participation of the cerebellum in the rhythmic discharge has been studied by gangs of silver-tipped electrodes placed on the surface of the exposed cerebellum. Responses have

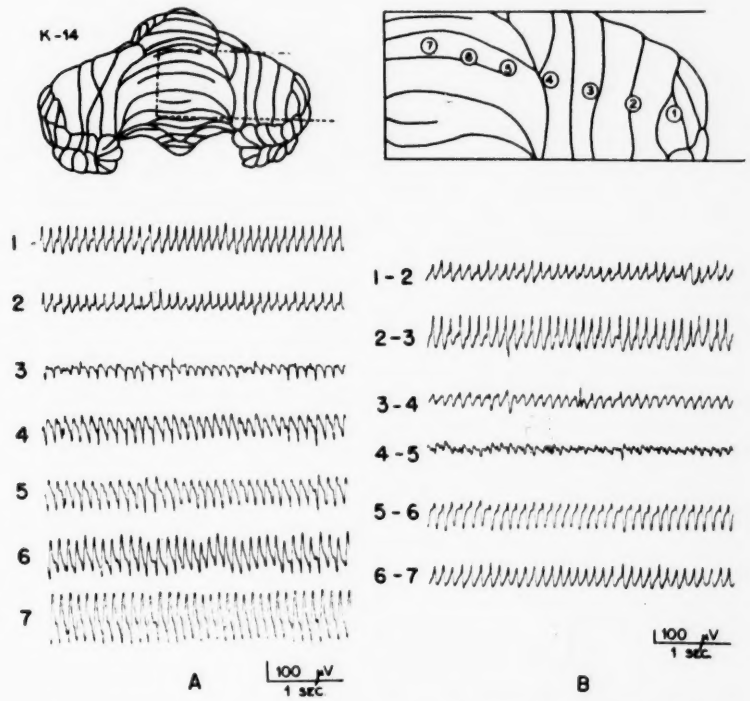

FIG. 1. (K-14). A cat, decerebrated, immobilized by succinylcholine chloride and artificially aerated, was given 2.5 mg. of strychnine sulphate one hour before this record. The electrodes were placed upon the cerebellar cortex as indicated in the enlarged sketch of the exposed cerebellum at the right. The distance between recording electrodes was 2 mm. The traces (A) at the left are monopolar recordings of the activity, which is seen to vary from vermis to cerebellar hemisphere but to be present throughout. In the traces (B) at the left are bipolar recordings from the same points as in (A). In all illustrations the vertical lines in the right lower corner indicate the stated voltage calibration, and the horizontal line an interval of one second.

been noted from the superior and posterior parts of the cerebellum accessible to recording. The activity of the flocculo-nodular lobe and of the vermian lobuli I, II, III, IX, and X of Larsell[7] were not sampled.

In Figure 1 the activity of the lateral and vermian folia is shown in both monopolar (A) and bipolar (B) recording. The frequency of the discharges is the same in all traces in the monopolar recording. The amplitude is higher (approximately twice) in the vermis (pts. 5, 6, 7) than in the lateral lobules (pts. 1, 2, and 3). However, there is considerable variability in the voltage of the discharges. In the bipolar recording these disparities are even more pronounced. Many factors besides the topical location of the electrodes may be responsible for these differences—the orientation of the electrodes on the folia, the pressure of the electrodes on the cerebellar cortex which appears to be sensitive to compression, and the placement of an electrode over a sulcus. It is noteworthy that the polarity of the spikes is reversed in the vermis and lateral folia. In the bipolar recording (B) the point of transition is difficult to determine, in fact, it is not clear that there is out-of-phase activity. Bremer and Bonnet's[1] interpretation of the vermian potentials as discharges induced by afferent bulbo-spinal volleys would seem correct, but the hemispheral potentials appear greater than can be accounted for by diffusion or field effect. The amplitude differential does not vary topographically as one proceeds laterally in the manner expected if diffusion were the only factor, and, secondly, as will be shown later, the activity of the paramedian lobule is quite distinct from that of the more lateral folia of the cerebellum and adjacent folia of the posterior vermis. Further studies are required to solve this problem.

Effect of electrode orientation on the recording of cerebellar discharge on the folium. Four electrodes were placed on the pial surface in such a way that simultaneous linkages were possible either along the length of a folium or across the same or two adjacent folia. The interelectrode distance was the same in both directions. Under such conditions, usually, the transverse linkage exhibits a "convulsive" activity similar to that seen in "monopolar" recording, but the longitudinal linkage shows less synchronized discharge (Fig. 2).

This feature is particularly evident at the slower frequencies of the "strychnine waves" (10-18 cps.). It is present on all regions of the cerebellar cortex from which the convulsive activity can be recorded, both in intact and decerebrate preparations, but it seems more evident in the latter. Usually it remains a constant feature throughout the course of the experiment, but in two animals from the most medial folium of the lobulus ansiformis a spontaneous inversion has been observed. In these animals the

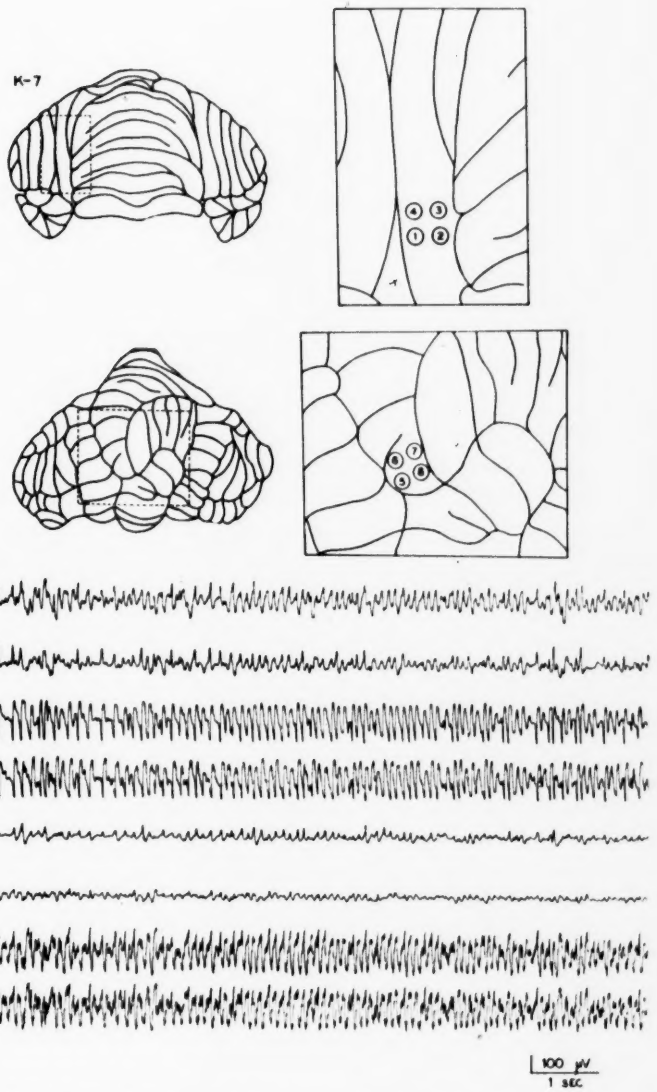

FIG. 2. (K-7). Traces from the cerebellum as indicated one hour and thirty minutes after the intravenous injection of 2.5 mg. of strychnine sulphate. The distance between recording electrodes was 1.6 mm. The longitudinal recordings from the folia are of much more amplitude than the transverse. This is true in both the vermis and hemispheres.

longitudinal linkage showed much more pronounced "convulsive" activity than the transverse one. In one animal the initial recording showed the usual transverse dominance, then the reverse appeared and persisted until the end of the experiment. Unfortunately, the transitional period occurred at a time when the electroencephalograph was turned off. In the other case the longitudinal recording was dominant initially and persisted so throughout the experiment. Electrode placements on other regions of the cerebellar cortex in the same animal gave the more usual characteristic, that is, a transverse dominance. It is interesting to note that this unusual response was recorded from the same region in the two animals, namely, the most medial folium of the lobulus ansiformis.

When the electrodes are so arranged that the activity across two adjacent folia can be compared with the activity along these folia, the feature described above is usually accentuated (Fig. 3).

Peculiarities of "convulsive" discharge of the paramedial lobule. The paramedian lobule seems to react differently to the other parts of the cerebellum which we have examined. Both in intact and decerebrate preparations the resting electrical activity of the paramedian lobule is practically the same as that of other cerebellar areas. After injection of strychnine, however, the paramedian lobule does not show such well-synchronized activity but a general increase in amplitude and numerous random fast spikes, usually positive or diphasic in polarity (Fig. 4).

The difference between this lobule and other part of the cerebellar cortex is particularly evident at the lower frequencies of convulsive activity. It is present in "monopolar" and in bipolar recording, either from one or from two adjacent folia.

Bipolar recording with one electrode on the paramedian lobule and another a few millimeters away, on a folium of the posterior vermis, shows marked high voltage "convulsive" activity, which may be slightly irregular.

In Figure 4 it is observed that the trace from one posterior vermian folium exhibits very little synchronized low voltage activity (linkage 7-8) and that recording from two adjacent folia of the paramedian lobule (linkage 6-5) has the same general characteristics as seen with "monopolar" technique. However, a high voltage, fairly well-synchronized activity, spiky in character, is apparent in the traces from electrodes on the paramedian and posterior vermian lobules (7-6 and 8-5).

DISCUSSION

The "convulsive" rhythmic activity of the cerebellar cortex seems to result from the bombardment of bulbo-spinal volleys upon the Purkinje

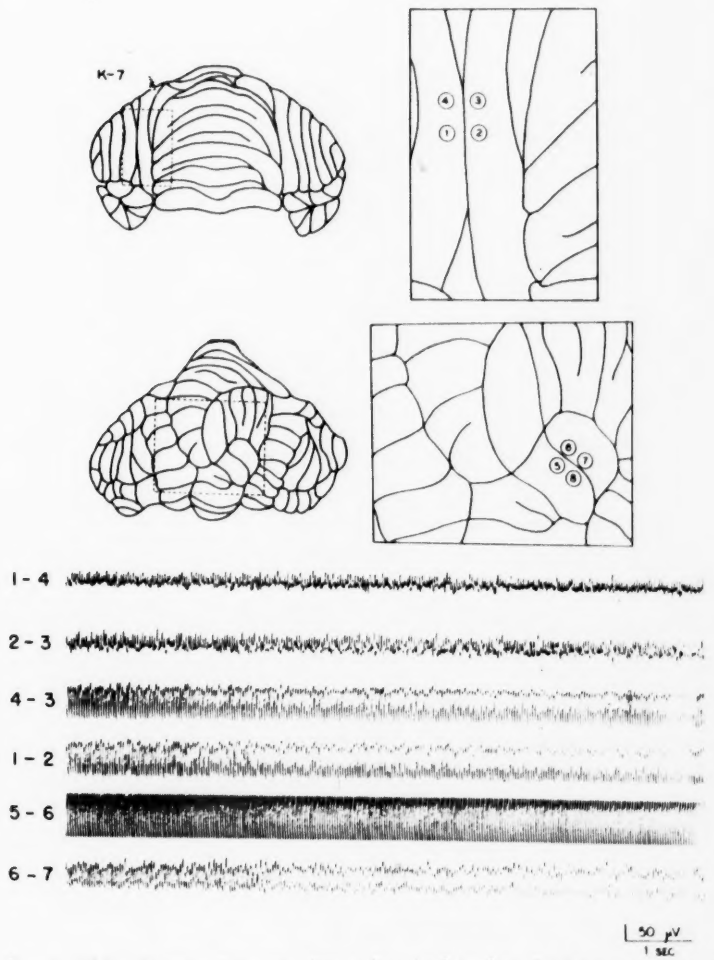

FIG. 3. (K 7). Traces taken one minute after the injection of 2.5 mg. of strychnine sulphate. The interelectrode distance was 2 mm. There is marked activity in the transversely placed electrodes and relatively little activity in the longitudinally oriented electrodes.

cells, the threshold of which has been lowered by the action of strychnine. The precise origin of these volleys has not been definitely ascribed to any particular anatomical nuclear group. Beaumont Johnson,[1] who has studied this aspect of the problem, concluded that the paroxysmal discharges were

present in practically all nuclear masses caudal to the brachium conjunctivum, especially the reticular nuclei, inferior olivary bodies, and vestibular nuclei. This suggests that several cerebello-petal systems in varying degrees may be implicated in the rhythmic activity. This multi-system discharge

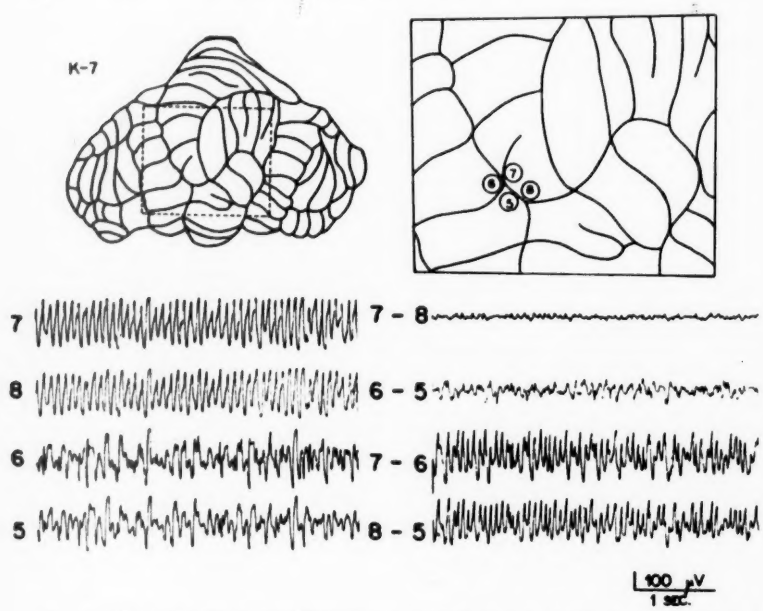

FIG. 4. (K-7). Taken approximately one hour after the injection of 2.5 mg. of strychnine, this trace shows monopolar recording (at the left) with approximately equal activity from the vermis and poorly synchronized and much less regular activity from the paramedian lobule. In the bipolar recording at the right, high voltage activity is seen in the records taken from the paramedian and vermian folia as described in the text. The interelectrode distance was 1.6 mm.

might account for the extensive involvement of cerebellar cortex and perhaps for the peculiarities of distribution which have been noted.

The finding that the paramedian lobule participates poorly in this rhythmic discharge does not appear to be explicable on the basis of cyto-architectural structure or anatomical connections. The exceptionally well-marked rhythmic discharge of the anterior lobe and vermis may be related to the richness and convergence of their afferent connections from the bulbo-spinal axis.

It seems evident that the differences in records made with electrodes longitudinally and transversely oriented to the cerebellar folia must be due

to the temporal and phasal relationships of the incoming volleys to the cerebellar cortex. It is possible that the phenomenon might be the result of cortical neuronal connections, so that longitudinal excitation is much more rapid than transverse. This concept is compatible with the known anatomical characteristics of the mossy fiber-granular system which courses from one end of the folium to the other.[8] However, this cortical thesis would require much slower conduction across the folium than one would expect.

A second explanation is based upon the assumption that the incoming volleys, synchronous at their bulbo-spinal origin,[1] being carried over fiber systems of different caliber at varying rates of conduction become slightly asynchronous at their termination in the cerebellar cortex. A topical arrangement of the endings of these systems in the cerebellar cortex would explain the different times of discharge of the Purkinje cells at the lips and at the convexity of the folium.

SUMMARY

The rhythmic synchronous discharge induced in the cerebellar cortex by the intravenous administration of strychnine is shown to occur in the superior, posterior, and lateral parts of the cerebellar vermis and hemispheres. The activity is minimal when recorded along a cerebellar folium and maximal when recorded across a folium or two folia. The significance of these findings is discussed.

REFERENCES

1. Bremer, F. and Bonnet, V.: L'activité convulsive du cervelet. J. Physiol. (Paris), 1953, *45*, 33-56.
2. Bremer, F. and Gernandt, B. E.: A micro-electrode analysis of the acoustic response and the strychnine convulsive patterns of the cerebellum. Acta physiol. scand., 1954, *30*, 120-136.
3. Gualtierotti, T. and Capraro, S.: Influenza degli stimoli periferici e centrali sulle variazioni dei potenziali d'azione del cervelletto. Arch. Sci. biol., 1941, *27*, 247-262.
4. Johnson, B.: Strychnine paroxysms in brainstem. I. Anatomical distribution. J. Neurophysiol., 1955, *18*, 189-199.
5. Johnson, H. C., Browne, K. M., Markham, J. W., and Walker, A. E.: Effect of strychnine on cat's electroencephalogram. Proc. Soc. exp. Biol. (N. Y.), 1950, *73*, 97-99.
6. Larsell, O.: The cerebellum of the cat and the monkey. J. comp. Neurol., 1953, *99*, 135-200.
7. Markham, J. W., Browne, K. M., Johnson, H. C., and Walker, A. E.: Rhombencephalic convulsive activity. Bull. Johns Hopk. Hosp., 1951, *89*, 442-467.
8. Marossero, F. and Garrone, M.: Convulsive activity in the cerebellar cortex. Electroenceph. Clin. Neurophysiol., 1952, *4*, 230.
9. Ramón y Cajal, S.: *Histologie du système nerveux de l'homme et des vertébrés*. Paris, Maloine, 1909-11. *2* vols.
10. Ruf, H.: Ueber die Beeinflussung experimenteller epiletischer Anfalle. Nervenartz, 1951, *22*, 437-439.

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THE EFFECTS OF PRECENTRAL LESIONS ON THE BEHAVIOR OF MONKEYS[¶]

Professor Fulton's important contributions to the study of the precentral motor cortex need no reviewing. At the time the studies here presented were undertaken in his laboratory, certain questions stimulated by his work repeatedly entered our discussions. This report is addressed toward some of these questions.

Bucy, in the introduction to the recent monograph on the precentral motor cortex, makes the following statement: "The editor regards the precentral motor cortex as the principal efferent or effector cerebral cortical mechanism by which the brain expresses its activity through the skeletal musculature."[1] Implicit in this statement is the suggestion that all learned behavior finds expression through efferents leaving the precentral region; that afferents relay signals to the "primary projection" cortices whence internuncials lead to the "association areas" which, in turn, play upon the precentral cortical areas. To be validated, this viewpoint must be supported by the following evidence: *anatomical*, showing a preponderance of separation between afferent and efferent tracts in the cerebrum; *electrophysiological*, showing a minimum of overlap between those areas responding (by "evoked potentials") to peripheral stimulation, and those areas which, when electrically excited, give rise to peripheral responses; *behavioral*, showing that learned behavior is impaired by injury to the more-or-less "final" common path. This paper deals with some experiments in the last category. The

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discussion will be concerned, as well, with experiments in the other categories.

Regarding the specific effects of lesions of the precentral cortex on behavior, three conceptions need clarification. The data giving rise to these conceptions are, in brief, as follows: a lesion of the precentral cortex interferes with patterned muscular contraction in some situations but these same or approximately similar patterns may be observed intact in other situations. Thus, an animal may fail to grasp a nail which holds together a box containing a peanut but grasps an equivalently thin wire composing the side of a cage while climbing; a patient may fail to close his fist on a tennis ball when asked to grasp it but will turn a doorknob in order to escape from a ward during a conflagration. Such data have given rise to two conceptions popular in clinical neurology: that the precentral cortex is implicated in "skilled movement"; that the precentral cortex is implicated in "voluntary movement." A third conception emphasizes the lack of effect of precentral lesions on the solution of problems provided some movement is possible. This conception looks, therefore, for an alternate approach to the specification of the relationship of the precentral areas to behavior and characterizes the impairment as an involvement of "postural mechanisms." In order to estimate the relevance of each of these conceptions, we reinvestigated the effect of precentral lesions on the patterns of response under several conditions. Opening a hasp box to obtain a peanut, discrimination of visually presented patterns, and the delayed reaction were used as quantitative behavioral indices. Neurological examination and observations of the animal's activity in his living quarters and in a relatively free environment provide background material against which the experimental data can be interpreted.

Some questions regarding the nature of the precentral lesions affecting behavior were also asked. Does locus of lesion within the precentral areas make a difference? Is extent of lesion an important factor? Is the decrement in performance of a limb contralateral to a lesion increased when that lesion is made bilateral? Is the effect of lesion dependent on removal of tissue or the result of "irritative" scar at the borders of the removal? The experiments reported suggest answers to these questions.

MATERIALS AND METHODS

Nine immature rhesus monkeys were used in these experiments. Eight of these animals received one or another resection of the precentral agranular cortex, the ninth was given multiple implantations of aluminum hydroxide cream over this cortex.

SURGICAL METHODS

Under intraperitoneally administered barbiturate anesthesia and using aseptic technique, a frontal osteoplastic craniotomy was performed through a coronal incision. The bone flap was hinged on the temporal muscle, the dural flap based on the sagittal sinus. The frontal cortex was exposed from the arcuate to the intraparietal sulcus, from the midline to the Sylvian fissure. Subpial ablation of the appropriate cortex was carried out through a pial incision and with a 19-gauge needle suction tip. The anterior removals included the posterior bank of the arcuate sulcus; the posterior removals included the anterior bank of the central fissure. All removals extended into the superior bank of the calloso-marginal sulcus. The extensive lesions involved all of these "buried" areas. Hemostasis was accomplished by temporary packing with cottonoid pledgets and waiting, rather than by cautery. For the "irritative" lesion, aluminum hydroxide cream was placed in five one-centimeter silver discs and these were distributed over the lateral and medial frontal agranular cortex and the dura closed tightly over them. Interrupted silk closure was routine. Bilateral procedures were carried out in two stages, separated by a 7- to 8-month interval.

BEHAVIORAL METHODS

Experimental subjects were observed in their living cage at least twice a day for 15 minutes and in a large enclosure once a day. They were observed in a relatively free situation; in addition, their reaction to threat and to feeding were noted. Their manipulations of food, of sticks, of the cage and enclosure walls during climbing, and their locomotion were recorded. Neurological examinations were performed on the animals while they were restrained in a neurological chair. At least two observers compared their findings in most instances.

Quantitative behavioral measures, made in a modified Wisconsin general testing apparatus designed for primates,[15] included timing of the opening of a simple latch box. This box, approximately 5 by 8 cm. is closed by a sliding metal lid which is locked by a 2" nail inserted through the lid into the side of the box. To open the box (which contains a peanut during the test trials) the monkey has to grasp the nail, pull it out, push the lid back, and take the peanut from the box. These maneuvers have to be performed in the order stated to accomplish the trial. The mean of the time taken in 30 consecutive trials was used as an index of performance. Thirty trials per day were given until stable performance was reached preoperatively; postoperatively, 30 trials per day were given for five days following surgery and then five days each month. Motion pictures were taken both pre- and postoperatively in this situation, and these were studied when shown at regular and slow motion speed.

Another quantitative behavior measure recorded performance on the classical delayed reaction task. In this situation *two* cups appear before the monkey. Into one of these (*which* one is determined by a random sequence) a peanut is dropped in full view of the animal. Then an opaque screen is lowered, hiding the cups from view for 10 seconds. When the screen is again raised, the animal has to choose between two identical appearing, closed cups. Correct choice depends on the monkey's remembering which of the two cups had been baited 10 seconds before. The subjects were trained beginning two weeks postoperatively until they reached a performance level of 90 per cent on a hundred consecutive trials. The number of trials required to reach this

criterion was compared with the mean of the number of trials taken by 35 unoperated monkeys tested in the same manner.

Visual discrimination was also tested. This task utilized the same boxes as those used in the delayed reaction, but in this instance the boxes were closed by covers on one of which a black plus sign was painted, on the other, a black square. The peanut was invariably concealed in the box marked "plus" but the position of the "plus" was varied from box to box in random sequence. Thus, the task for the monkey was to choose the box marked plus; the numbers of trials taken by the operated animals to accomplished this in 90 out of 100 consecutive trials was compared with the mean score taken to reach the same criterion by 44 unoperated control subjects.

ANATOMICAL METHODS

Following the completion of the neurological and behavioral examinations, all the animals were sacrificed, the brains perfused with saline and formalin, dehydrated in alcohols, and imbedded in celloidin. In animals 2400 and 2345 the operated region was exposed under ether anesthesia and excitable points were identified and mapped in cortex and exposed white matter. Serial sections at 25 micra, were made, every tenth section saved and every other saved section stained with thionin. From these sections the extent of lesion was orthogonally reconstructed onto graph paper; reconstructions and representative cross-sections demonstrating depth of resection are presented in Figure 1. Retrograde thalamic degeneration was plotted and is also shown in this figure.

RESULTS

EXPERIMENT 1. UNILATERAL LESIONS

Five monkeys were tested preoperatively, operated upon, and retested. Two of these animals (*2428* and *2427*) received extensive unilateral resections of the dorsolateral, frontal, agranular cortex; in one animal (*2376*), the unilateral resection was restricted to the posterior; in another animal (*2434*), to the anterior portion of the frontal agranular cortex. A fifth animal (*2418*) received a resection of the greater portion of the frontal agranular cortex, including that of the anterior cingulate gyrus.

A preliminary report of the results of the neurological examinations has been presented elsewhere.[1] Observations of the movements of the animals in the home cage and the large enclosure under "free" conditions and in feeding and threatening conditions are summarized; performance in the formal testing situation is described in detail below.

Subtotal resection of the frontal agranular cortex (2376 & 2434)

In the free situation, a paucity of spontaneous and associated movements of the extremities contralateral to the lesion was noted for two weeks to one month postoperatively. Anterior lesions affected especially the movements of the proximal musculature; movements about the shoulder and hip were

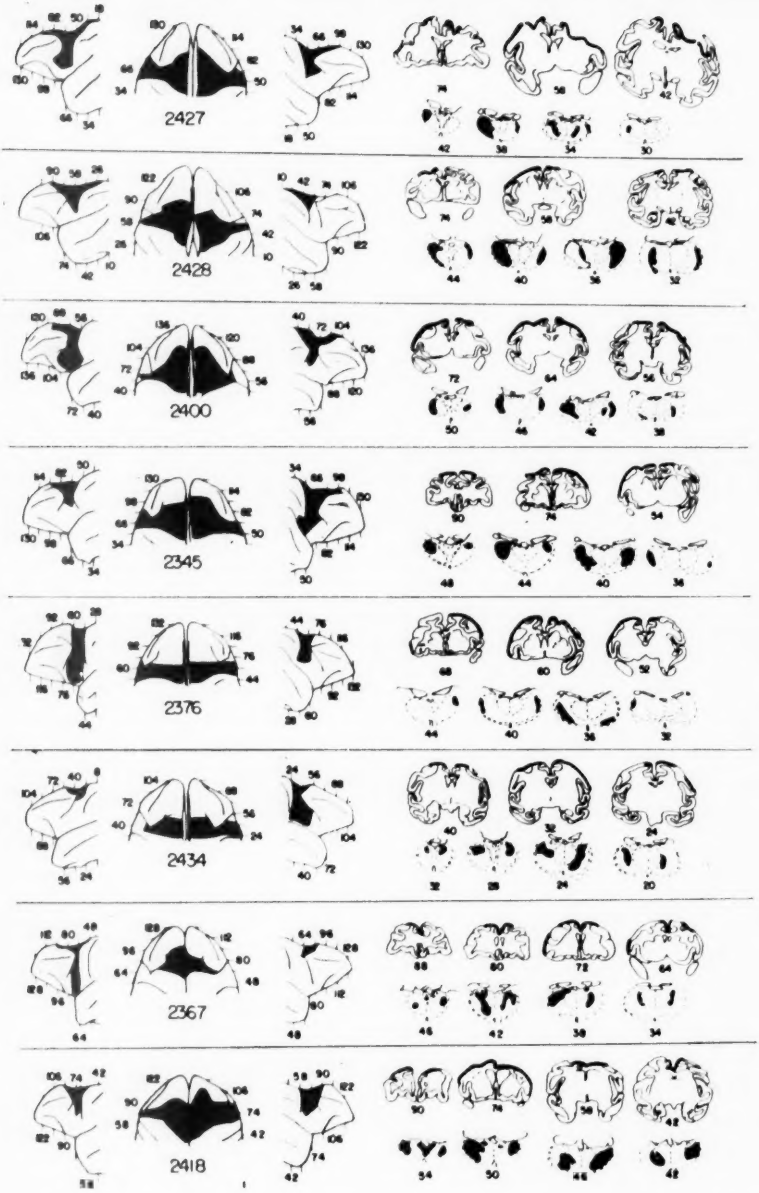

FIG. 1. Reconstructions and representative cross-sections through lesion and thalamus of brains of the animals used in this experiment. Black indicates locus and extent of ablation of cortex (left side of figure) and locus and extent of retrograde thalamic degeneration (right side of figure). Numbers refer to subject and to the actual cross-section from which diagram was made.

awkward when they were present at all. Posterior lesions, on the other hand, affected movements of the distal musculature: especially flexion of the digits in climbing was impaired. When in a threatening or feeding situation, the affected movements would be present initially but faded as the situation continued. However, these effects were not detected beyond the first postoperative month.

In the latch box test situation these animals showed a decrement in performance only during the first postoperative week. Whereas their performance with the hand ipsilateral to the lesion continued at the preoperative rate of under 2 sec. to accomplish a trial, performance with the hand contralateral to the lesion took between six and seven seconds during this period. The performance difficulty differed for the two subjects, however. The animal with the posterior resection was clumsy in manipulating the nail and the box cover; the animal with the anterior resection showed clumsiness in bringing the arm to the latch box and occasionally in "letting go" the nail or box cover preparatory to making the next movement in the sequence. After the first postoperative week, these difficulties were no longer observed and performance time became equal for both extremities.

Extensive resection of the frontal agranular cortex (2428 and 2427)

In the free situation a hemiparesis of the limbs contralateral to the lesion was consistently noted during the first postoperative month—i.e., the animals rarely used the affected extremities; when movements did occur, they were gross, clumsy, and of short duration. During the second postoperative month the affected extremities were moved in association with climbing and running movements of the other side; however, when only one extremity was required for the performance of an act, the extremity ipsilateral to the lesion was consistently employed. This preference persisted for three months after which it receded gradually and disappeared, first in the threatening and feeding situations. In these situations the affected extremities were used after the second postoperative week to accomplish prehension of, or escape from, the stimulus object.

In performing the latch box task no effect of the resection was observed when the animal used the arm ipsilateral to the lesion. However, when only the arm contralateral to the lesion was available for the task performance, *no trial was accomplished within six months following surgery*. Only occasionally would the subject make an attempt to dislodge the nail and open the box; on each occasion the movements were executed in a gross manner precluding accomplishment of the trial. For the most part, the animal just sat quietly or began to play in the testing cage rather than manipulate the latch. As soon as the arm ipsilateral to the resection was

TABLE 1.

TWO-STAGE BILATERAL RESECTIONS OF FRONTAL AGRANULAR CORTEX									
Animal	Lesion	Pre-2nd op.		1 Week	1 Month	2 Months	3 Months	4 Months	5 Months
2400	Extensive Dorsolateral	L. 1.4 R. 1.4	RIGHT SIDE OPERATED	L. - R. 6.7	L. 11.4 R. 11.0	L. 4.1 R. 3.5	L. 3.2 R. 3.4	L. 2.2 R. 4.7	L. 2.0 R. 2.1
2345	Extensive Dorsolateral	L. 1.9 R. 2.7		L. - R. 4.3	L. . R. 13.5	L. 16.9 R. 4.3	L. 6.9 R. 4.1	L. 5.1 R. 3.3	L. 3.4 R. 3.2
2376	Precentral	L. 1.9 R. 3.9		L. 3.7 R. 5.1	L. 1.7 R. 2.1	L. 1.4 R. 3.4	L. 1.8 R. 2.4	L. 1.7 R. 2.0	
2434	Anterior	L. 2.6 R. 2.1		L. 4.2 R. 2.3	L. 3.2 R. -	L. 2.8 R. 1.9	L. 2.3 R. 2.2	L. 2.3 R. 2.5	
2367	Anterior plus Cingulate	L. 1.4 R. 1.4		L. 4.4 R. 1.6	L. 3.0 R. 2.2	L. 2.0 R. 1.6	L. 1.7 R. 1.7	L. 1.6 R. 1.7	

"IRRITATIVE" UNILATERAL, LEFT 2398									
	1 Month	2 Months	3 Months	4 Months	5 Months	6 Months	7 Months	8 Months	9 Months
L.	2.1		2.0	1.6	1.8	2.1	1.8	2.0	1.8
R.	2.6	2.8	2.5	2.4	4.2	11.0	10.0	22.8	11.1

released from restraint, however, testing with this extremity proceeded at speeds indistinguishable from those obtained preoperatively. In the seventh to ninth postoperative month, clumsy attempts were made by the animals to open the latch with the affected extremities. Performance scores of 16 to 30 sec. were recorded, but difficulty in maintaining the animal's attempts to perform a series of trials with the affected hand attended each session. Consistent performance with this extremity was thus never re-established in these animals. The grave deficit shown by all animals made it difficult to evaluate any difference between them (differences which might be attributed to the additional resection of the cingulate cortex in one of them).

Aluminum hydroxide cream implantations of the precentral agranular cortex

During the fifth postoperative week, this animal (2398) began to have Jacksonian convulsions in the right side of the face, contralateral to the lesion and spreading quickly to involve the entire right side. Occasionally the seizures would become generalized. Seizures occurred most frequently during the third and fourth postoperative months; at this time, from four to a dozen seizures per day were noted. The feeding and threatening situations almost invariably induced convulsions. As reported for other "irritative" frontal lesions,[12] the monkey soon became "conditioned" so that when a stick was shown him, the seizure activity would be initiated. Beginning in the fifth postoperative month these generalized seizures became less frequent; instead, an almost continual 3-4 per second rhythmic activity of the right arm and hand was present whether or not the arm was engaged in some activity. This "tremor" persisted but became less noticeable toward the end of the first postoperative year.

As indicated in Table 1 the scores of performance of the latch box task reflect the appearance of the "tremor" but do not correlate with the onset of Jacksonian convulsions. Time scores taken for the affected extremity are markedly increased after the fifth postoperative month and continue to reflect the awkwardness of performance for the remainder of the time the animal was tested.

TABLE 1. *Upper:* Results of the two-stage bilateral procedure. Numbers indicate the mean of time scores of 150 consecutive trials. Dash indicates that no score was obtained, usually because the subject failed to manipulate the latch box.

Lower: Results of the irritative scarring procedure. Time scores indicated as in upper portion of table.

Electroencephalographic abnormalities (marked slowing and spike activity) began to appear in the left central scalp leads during the second postoperative month and persisted thereafter, with gradual decline, for the entire postoperative year. The appearance of the electrical abnormality correlated with the appearance of convulsive episodes, not with change in test performance.

EXPERIMENT 2. BILATERAL LESIONS

Seven monkeys served as subjects for this experiment. Four of these (*2427, 2428, 2434, 2367*) had been used in Experiment 1. Since consistent latch box performance with the affected extremity had not been re-established by monkeys *2427* and *2428*, they were used following the second surgical procedure only to study performance of the delayed reaction and visual discrimination tasks. Two other subjects (*2400* and *2345*), with somewhat more superficial but equally extensive resections of the precentral agranular cortex, were trained in the latch box situation beginning six months after the initial unilateral procedure. When consistent performance of this task was established with both extremities, the second surgical procedure was undertaken. A similar program of testing was pursued with another monkey (*2367*) with an ablation of the cingulate cortex in addition to an anterior precentral lesion. In this animal the cortex surrounding the central fissure was spared in order to assure the possibility of some performance in the test situation. Subject *2376* with a posterior and subject *2434* with an anterior lesion were used to compare the effects of bilateral subtotal resections. Before the second surgical procedure was undertaken, these animals had re-established consistent latch box performance following the unilateral procedure as described in Experiment 1.

Protocols of the neurological examinations of these animals will be presented elsewhere. Observations of the movements of the animals in the home cage and the large enclosure under "free" conditions and in feeding and threatening conditions are summarized; performance in formal testing situations is described below.

Subtotal resections of the frontal agranular cortex (2376, 2434, 2367)

In the free situation a paucity of movement was observed in the extremities contralateral to the second lesion for one, or at the most two, weeks. When these extremities were used, paresis was noted; e.g., the animal did not suspend itself from the cage wall for as long a period with the affected extremity. After the first week or two no difference between the two sides could be distinguished. However, the animals continued to tire easily when running (in the threatening situation) for about six months after the second

operation; no difference between the two sides could be seen. Nor was a difference between the effects of anterior and posterior subtotal resection as marked as that observed after unilateral ablation. Nevertheless, posterior resection affected primarily the movements of the hands and feet as in climbing; anterior resection affected primarily running and hanging from cage walls and ceiling.

Records obtained in the latch box situation appear in Figure 1 (*2370, 2434, 2367*). Note that only during the first postoperative week was performance with the hand contralateral to the second operation defective. Even during this period, the problem was solved within twice the time taken preoperatively. Note also that the posterior subtotal resection and only this one affected performance of the ipsilateral hand as well as that of the contralateral hand. Such exacerbation of a defect which had subsided during the months following the first resection is still more noticeable with extensive resections as will be seen below. All in all, there is remarkably little effect of these lesions on performance of the latch box task; and this finding is not altered when the cingulate cortex is added to the resection.

Extensive resections of the precentral agranular cortex (*2400, 2345, 2427, 2428*)

Both with regard to general observations and test behavior, the effects of extensive precentral resections were more drastic and more lasting. In the free situation, the animals with these resections fell frequently to the side contralateral to the second operation. For a month to six weeks they used the extremities contralateral to the lesion sparingly. Instead of running in the threatening situation, they would "lope" somewhat awkwardly. They were never observed to jump from wall to wall following the second surgical procedure. Nevertheless, in both the feeding and threatening situations, movements were executed in appropriate sequences to accomplish getting food into the mouth or in fending off a stick. These movements were carried out slowly, however, and the animals tired easily; they could also be caught easily even six months after the second operation.

Performance of the latch box task with the hand contralateral to the lesion could not be obtained at all for a month in one subject, for over six weeks in another. Scores obtained with the hand ipsilateral to the resection also suffered markedly, as can be seen from Table 1. Performance did not return to preoperative levels during the five months of testing but stabilized for one animal during the second month and for the other animal during the fifth postoperative month at slightly longer values than the preoperative. Performance was thus impaired but not abolished; impairment consisted in

awkwardness of movement resulting in longer time scores. The sequence of acts was unimpaired.

The monkeys with extensive bilateral precentral resections performed the delayed reaction and visual discrimination as well as did the unoperated controls. Thirty-five unoperated monkeys tested in the delayed reaction procedure as outlined took a mean of 380 trials to reach criterion. The operated subjects of the present experiments took 210 and 270 trials to reach criterion. Forty-four unoperated monkeys tested in the visual pattern discrimination procedure as outlined took a mean of 375 trials to reach criterion. The operated subjects of the present experiment took 150 and 310 trials to reach criterion. Clearly, there is no deficit in learning of the delayed reaction or of the visual pattern discrimination following extensive resection of the precentral agranular cortex.

DISCUSSION

It is clear to us from our experiments that extreme views of the rôle of the precentral gyrus cannot be maintained. Neither the idea that the "motor" cortex is "more concerned with the maintenance of excitability and the regulation of postural reflexes than with the excitation and control of finely integrated adaptive movements,"[9] nor the conception that this cortex serves as the sole or even "principal cerebral efferent or effector mechanism by which the brain expresses its activity,"[3] accounts satisfactorily for our observations. Nevertheless, both statements, especially when taken in the context of the discussions from which they were excerpted, have considerable usefulness in pointing out problems that must be faced in any evaluation of the effects of precentral lesions on behavior.

Observations of the movements (such as manipulating food) of the monkeys with extensive precentral resections in the free and the more structured situations cannot all be classified as impairments of postural mechanism. The increased time scores made by these animals in the latch box problem, confirming Lashley's own earlier results, make such an interpretation inadequate. Furthermore, according to Lashley's view "impulses descending from the precentral gyrus do not initiate the finer adaptive movements through the lower motor neurons, but only 'prime' these cells so that they may be excited by impulses from other sources."[9] Although Lloyd's work on the pyramidal system of cats[10] does indicate an indirect pyramidal influence on the motoneurons of the ventral horn, the recent work of Bernhard and his co-workers[2] shows that impulses from the motor cortex do indeed directly impinge upon and excite motoneurons *in the monkey*. Lashley's conception was originally derived from experiments on

rodents,' animals which show little motor defect with cortical ablation. Perhaps assigning the motor cortex a predominant rôle of reflex regulation of postural mechanisms is more easily envisaged in the more primitive mammals, but this view is unlikely to apply to primates.

On the other hand, the evidence that primates with extensive precentral resections learn and perform delayed reaction and visual discrimination tasks without impairment suggests the necessity for a revision of the conception that the precentral pyramidal system need be the principal cerebral efferent mechanism or even the "intermuncial" between cerebral mechanisms involved *in problem solving behavior* and the orgahism's effectors. The origin of pyramidal tract fibers in regions other than the precentral cortex, the evidence of efferents from the optic cortex and from the supratemporal auditory cortex,' the efferents from Ammon's formation (the fornix) as well as the efferents from the anterior frontal (Arnold's bundle) and the temporal cortex (Turck's tract), must be assigned equal importance to precentral efferents when *selective* effects on behavior follow the disruption of each of these systems." Nonetheless, one cannot dodge the issue that the selective effects resulting from the resection of the precentral gyrus is particularly devastating to an organism's *effector* mechanisms. Thus, extensive precentral lesions can be seen to interfere with performance of almost any task given to the primate provided the appropriate measure—e.g., time required for the manipulation—is made. However, in an analysis of the meaning of our measurements and observations, we must take into account the things undisturbed as well as those disturbed. When this is done, it becomes obvious that those actions involving discrete movements or "skills" are the ones most susceptible to disruption by precentral lesions. However, the disruption is limited to the effectors controlled by the portion of precentral cortex involved in the lesion—no general "forgetting" of the problem solution ensues. Thus, skills are interfered with by precentral lesions, not lost through excision of the locus of the "habit." These results are analogous to those following restricted resections of the optic cortex of the occipital lobe. Whereas the latter produces scotomata in the visual field, lesions of the precentral cortex may be said to produce scotomata of action. In vision, no decrement in the retention of learned discriminations follows subtotal occipital resections; in motor activity, no decrement in the retention of problems solution can be determined following precentral resections.

But what of the idea that "will" as well as skill is affected by the precentral lesions? Experimental resections restricted to the precentral cortex of man[—] suggest that such lesions do *not* interfere with what is commonly called "voluntary" activity; in fact, the clinical syndrome differs little from that described here for the monkey. It is likely that the more severe

disturbance found in man which is characterized as a "loss of voluntary movement" is due to deep frontal lesions involving the internal capsule. Such lesions disturb not only precentral but a variety of other cerebral mechanisms.

Regarding the effects of different precentral lesions, some reconciliation of divergent views may also be suggested. Woolsey's[5] precise maps of the responses obtained from electrical stimulation of the precentral cortex show that the posterior portions of this area, in and adjacent to the central fissure, are concerned with the control of appendicular musculature, while the anterior portions are more concerned with axial musculature. Our observations show that posterior lesions do, indeed, affect the precision of the animal's hand movements in the latch box more than do anterior lesions. The latter, on the other hand, affect primarily the movements around the shoulder and hip muscles. Former conceptualizations of the difference between the effects of anterior and posterior lesions in terms of "discrete" vs. "coordinated" movements may thus be understood since movements carried out primarily with the distal portions of the extremities *are* more discrete than those involving primarily the larger axial muscle groups. The other differences which are presumed to exist between anterior and posterior lesions have been discussed elsewhere.[1] However, coordination is involved whether discrete or more massive movements are or are not concerned—thus, the conceptualization in terms of somatotopy, which has been presented here, is preferred.

The extent of precentral cortex resected is important as shown by the relatively small and transient effect of subtotal lesions as compared with the greater and more lasting effect of the extensive ablations. However, recourse to a simple notion of "mass action" is ruled out by the apparent lack of increased decrement in performance of the latch box problem when anterior cingulate ablation is added, either to a subtotal or to a total precentral resection. Within the precentral agranular isocortex, when a unilateral lesion is made bilateral, there is an effect on the extremity ipsilateral to the second lesion—so effective "mass" is distributed bilaterally within the cortex. Lesions of comparable extent in other cortical fields studied produce either no observable motor defects (frontal granular, temporal, striate, peristriate, and limbic fields) or minimal transitory defects (postcentral and parietal fields). The recent study of Semmes and Chow[6] in which the effects of lesions of all the cortex except the precentral agranular were found to be similar to those of precentral motor cortex ablation—except in the duration of effect—implies a lack of specificity in the function of different cortical areas in motor behavior. Although other regions of the cortex can be implicated in motor behavior, this may also be said of total

de-afferentation of a limb. By applying a diversity of appropriate measures, the specificity of any such deficit may be elucidated. Such techniques used by Fulton and his co-workers[6] in analyzing motor function have led to the demonstration of defects in posture, the various forms of tactile and proprioceptive placing, hopping, resistance to passive limb manipulation, palpable muscle tone, the degree and *form* of tendon reflexes, influence of body and head position, the alterations in stimulation conditions required to elicit grasping, and other detailed neurological tests related to motor function which in our experience clearly differentiate the motor defect following frontal agranular lesions from that seen with any other cortical lesion.

There have been suggestions[7] that the effects of lesions are due solely to irritative scars at their borders. Comparison of aluminum hydroxide cream lesions with those of ablations in the present experiments suggests that the two types have different effects—that both these effects might be conceived as a disequilibrium of function, but that a distinction can be made. Resections impair performance, i.e., in a particular situation, the repertory of action available to an animal with precentral resection is more limited than the repertory available to an intact animal. However, within that repertory, a fairly stable, albeit limited, performance of tasks results. The animal with aluminum hydroxide cream implantation, on the other hand, shows impairment in a larger spectrum of behavior by the pervasiveness of the repetitive muscular contractions which persist whether he is active or inactive, whether he is performing a task requiring skill or one where only grosser movements are concerned. Thus, the animal's limitation in a particular task may or may not be as severe as that of the subjects with resection, and often fluctuates to a considerable extent for reasons that have not as yet been determined.

In conclusion: we feel that certain tentative answers can be given to the questions which initiated these experiments and were posed in the introduction. Extent of ablation is an important consideration in evaluating the effect of a precentral lesion. Effects of unilateral ablations are enhanced when the lesion is made bilateral. Effects of ablation cannot be attributed to "irritative" scarring at the border of such lesions since the effect of "irritative" lesions per se can be distinguished from those of ablation.

Precentral lesions interfere especially with skilled acts; the acts are not lost, however, through excision of the locus of a "habit"; rather, a scotoma of action may be said to result. Thus, the extreme conception that the precentral cortex is the principal efferent system by which the brain expresses its activity is modified in favor of the conception that the precentral cortex modulates a variety of reflex mechanisms basic to action. The numerous anatomical studies on the afferent and efferent relations of the somatic

"sensory" and "motor" areas of the monkey cerebral cortex have recently been supported by electrophysiological demonstrations of efferents[5] and afferents[6] to both of these regions. The "unity" of the "sensorimotor" cortex is further emphasized by the remarkable constancy of proximity of somatic "sensory" and "motor" fields and the absence of intercalated "association" areas in all mammals. Although it is recognized that the preponderance of afferent and efferent fibers differ in the precentral and postcentral regions, we believe that their close anatomical relationship should be emphasized rather than any conceptualization based on analogy with the dorsal and ventral roots of the spinal cord.

Experiments in both monkey and man indicate that resections limited to the precentral cortex do not interfere with behavior of the type usually described as "willed." Rather, we think it possible that deep lesions involving the internal capsule are responsible for such grosser changes in behavior by interrupting a variety of cerebral mechanisms. Thus, the clinically derived conception that the precentral motor cortex serves "skilled action" is corroborated; it is clear, however, that this cortex is not the locus of a "habit" or of a mechanism basic to any performance of the skill, but rather that precentral lesions result in a scotoma of action which interferes with the skill. On the other hand, the clinically derived conception that the precentral cortex is involved in "willed action" is considerably modified; deep lesions involving not only precentral, but also additional, cerebral mechanisms are thought to be responsible for the grosser defects in behavior which led to this conception.

SUMMARY

Ablation of the precentral agranular cortex was found to interfere especially with skilled acts as measured by time scores in performing a latch box task. Lesions restricted to the posterior portion of this cortex caused a greater defect in digital dexterity than anterior lesions which more markedly affected the more proximal musculature. Total ablation caused the most marked defects. Visual discrimination and delayed response performance were unaffected by precentral ablations. Bilateral ablations exacerbated the effects of unilateral ablation and caused a renewed defect on the side ipsilateral to the second operation. The effects of ablation cannot be attributed to "irritative" scarring at the border of such lesions since the effects of "irritative" lesions per se can be readily distinguished from those of ablation. It is concluded that the motor defect in precentral ablations is not due to acts lost through excision of the locus of a "habit," but rather that scotoma of action result.

REFERENCES

1. Berman, A. J., Kruger, L., and Fulton, J. F.: Recovery of function following lesions of frontal agranular cortex in the monkey. Trans. Amer. neurol. Ass., 1954, 178.
2. Bernhard, C. G., Bohm, E., and Petersen, I.: Investigation on the organization of the corticospinal system in monkeys (macaca mulatta). Acta physiol. scand., 1952, *29*, 79.
3. Bury, P. C.: *The precentral motor cortex*. Urbana, University of Illinois Press, 1949, p. 3, p. 355.
4. Ferrier, D.: *The functions of the brain*. London, Smith, Elder and Co., 1876, p. 323.
5. Foerster, O.: Symptomatologie der Erkrankungen des Grosshirns: motorische Felder und Bahnen. In Bumke u. Foersters *Handb. Neurol.* Berlin, J. Springer, 1936.
6. Fulton, J. F.: *The physiology of the nervous system*. 3d ed. New York, Oxford University Press, 1949.
7. Hebb, D. O. and Penfield, W.: Human behavior after extensive bilateral removal from the frontal lobes. Arch. Neurol. Psychiat. (Chicago), 1940, *44*, 421.
8. Lashley, K. S.: Studies of cerebral function in learning. The motor areas. Brain, 1921, *44*, 255.
9. Lashley, K. S.: Studies of cerebral function in learning. V. The retention of motor habits after destruction of the so-called motor areas in primates. Arch. Neurol. Psychiat. (Chicago), 1924, *12*, 249.
10. Lloyd, D. P. C.: The spinal mechanism of the pyramidal system in cats. J. Neurophysiol., 1941, *4*, 525.
11. Mahs, L. E., Pribram, K. H., and Kruger, L.: Action potentials in "motor" cortex evoked by peripheral nerve stimulation. J. Neurophysiol., 1953, *16*, 161.
12. Penfield, W. and Rasmussen, T.: *The cerebral cortex of man*. New York, Macmillan, 1950, p. 241.
13. Pribram, K. H.: Some aspects of experimental psychosurgery: the effect of scarring frontal cortex on complex behavior. Surg. Forum, 1951, *36*, 315.
14. Pribram, K. H.: Toward a science of neuropsychology: Method and data. *Current trends*. Pittsburgh, University of Pittsburgh Press, 1954, p. 115.
15. Pribram, K. H., Mishkin, M., Rosvold, H. E., and Kaplan, S. J.: Effects on delayed-response performance of lesions of dorsolateral and ventromedial frontal cortex of baboons. J. comp. physiol. Psychol., 1952, *45*, 565.
16. Semmes, J. and Chow, K. L.: Motor effects of lesions of precentral gyrus and of lesions sparing this area in monkey. Arch. Neurol. Psychiat. (Chicago), 1955, *73*, 546.
17. Woolsey, C. N. and Chang, H. T.: Activation of the cerebral cortex by antidromic volleys in the pyramidal tract. Res. Publ. Ass. nerv. ment. Dis., 1948, *27*, 146.
18. Woolsey, C. N., Settlage, P. H., Meyer, D. R., Sencer, W., Hamuy, T. P., and Travis, A. M.: Patterns of localization in precentral and "supplementary" motor areas and their relation to the concept of a premotor area. Res. Publ. Ass. nerv. ment. Dis., 1952, *30*, 238.

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THE MOST IMPORTANT STEPS IN THE DEVELOPMENT OF NEUROLOGICAL SURGERY†

It has been my good fortune to have followed the growth of neurological surgery from its inception, even before the term "neurological surgery" had come into use. For that reason, I regret a tendency among many men today to forget our predecessors and to withhold credit where credit is due the pioneers for the arduous task of initiating the work that has grown into a great specialty. Most men, certainly in America, believe that neurological surgery started in this country, which is not the case. Although it received its great impetus from the work of Harvey Cushing at Johns Hopkins, and subsequently at Harvard, the pioneer in this field was Victor Horsley of London who did his work at the National Hospital in Queen's Square and at University College.

As far back as the eighteen-nineties, Horsley[1,2,3] carried on fundamental research on the brain centers. He was the first to localize centers in the brain in his study by electrical stimulation of the cortex of a orang utang and, promptly applying these studies to localization in the human brain, he was able to localize brain tumors. He was the first to remove a spinal tumor successfully and in his epoch-making paper on the subject with Gowers[4] laid down the principles of spinal localization, to which little has been added to this day. He was the first to advocate cutting the posterior root of the 5th nerve for the cure of trigeminal neuralgia, as well as the first to undertake an operation on a pituitary tumor. Also, it was Victor Horsley who eradicated rabies from the British Isles by insisting that every dog brought into these countries should be quarantined for six months; that law is still in force today. All these things he did in spite of technical methods we consider very crude nowadays and without the many aids we have come to believe indispensable. When asked why he undertook procedures never heard of before, his reply was characteristic of all pioneers: "How are the people who come after us going to know how to do these things if somebody doesn't begin?" It was with this great master that I had the good fortune to have received my training.

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When I returned from England in 1908, only two men were doing neurological surgery in America, Harvey Cushing[1] at Hopkins and Charles Frazier[2] in Philadelphia. At this time it was such a discouraging field that few men cared to go into it. Because of the unsatisfactory results, it was very difficult to find assistants or even to interest men in the future possibilities of the work. This was understandable when the popular saying was, "Most brain cases die."

That was forty-seven years ago, and the vast change which has come about since then is evident when we consider the great number of men in the field today. In the United States alone there are over 500 qualified neurological surgeons, and a similar growth is taking place all over the world. The question, therefore, arises, "What were the important factors that have brought about this great change?"

The first was the realization that a new technique must be developed; and the meticulous methods that are routine in every neurosurgical clinic today came into being. While many contributed to this, I think everyone will agree that the one man more responsible for this development than anyone else was Harvey Cushing. Thanks to his technique, many of the early difficulties and complications are no longer encountered. Prior to the adoption of the Cushing technique,[3] in cases of increased pressure due to trauma or tumor, the brain would often herniate through a wound and form that ghastly complication—a cerebral fungus. This has become a thing of the past, and today many young neurosurgeons hardly know the term or have seen the condition.

In those early days, the handling of cerebrospinal fluid was not understood, and I can recall vividly a meeting at Dr. Frazier's clinic when one entire session was devoted to the advisability of removing cerebrospinal fluid by puncturing the ventricles in the course of a cranial operation. Today this procedure is a routine measure, and we have learned how it may transform a difficult, sometimes desperate, situation into one readily managed.

The next important step was the realization that the surgeon must be a trained neurologist, able to study and evaluate the clinical picture himself. Whereas formerly he had been dependent on the neurologist for his diagnosis, this could not continue if real progress was to be made. This independence on the part of the surgeon has not been universally accepted, however, and there are still centers where the neurologist rules. Strange to say, this is the case in the very institution where neurological surgery had its birth—the National Hospital in London where Victor Horsley did his epoch-making work.

But progress continued to be slow until 1918, when the discovery was made which completely revolutionized the field. The introduction of ventriculography by Walter Dandy[5] changed the entire picture. Few of you recall the era before 1918 when day after day, in spite of the most careful neurological examination, we had to acknowledge that the patient was operated upon for a tumor which proved not to exist. Those years were so discouraging that I wonder now how we lived through them, surviving the daily ordeal and persevering.

Let me illustrate the great change that resulted from this discovery. About 1920 I published with my late colleague, Dr. Sidney I. Schwab of St. Louis, and read before the American Neurological Association our diagnostic results over a period of eight years. Rather proudly we reported that an accurate, localizing diagnosis had been made in 55 per cent of cases. With the free use of air injection, however, conditions changed completely. Though not immediately adopted, it was not very long before clinics all over the world reported localization in over 95 per cent of cases.

I observe with much regret that there is a growing tendency not to make use of air injection as freely as in the past, and that the risks, to which Dandy and others drew attention, are often disregarded. One of the most important of these is allowing too long an interval to elapse between the air injection and the craniotomy. The operation should follow the air injection as soon as possible.

But even after we had this valuable addition to our armamentarium, the problem of bleeding caused our greatest difficulties. The need, however, has a way of bringing the solution. The development of transfusion and the introduction of citrated blood by Lewisohn[6] proved to be a great advance over the cumbersome, direct transfusion methods devised by Crile.[7] But transfusion methods in the early days were very different from those in use today. Then, we had to collect blood in waxed cylinders—the so called Kimpton tubes—and inject it directly into a vein. Rarely were we able to give a patient more than 500 cc., for the day of blood banks had not yet dawned. I can recall vividly, after these many years, patients with benign meningiomas who would be alive today if we had been able to give repeated transfusions as is customary now.

The control of hemorrhage has always been a fundamental problem, and even after blood had been made available further methods had to be devised to control hemorrhage. The very useful silver clips devised by Cushing[8] have now been almost entirely replaced by the introduction, also by Cushing, of electrocoagulation.[9] This has made it possible to make incisions into the brain and excise large areas with impunity. After the introduction of air injection we were able to diagnose deep seated lesions, yet often dared

not attack them, fearing we could not expose them safely. Electrocoagulation completely changed this.

The next important step forward was the discovery by Cohn[5] and his associates at Harvard of the blood derivatives, and the development of Gelfoam for the control of bleeding.

These technical problems having been mastered, further progress was made possible, and the last fifteen years have brought developments along various lines. The discovery of angiography by Moniz[6] has thrown new light on a number of conditions hitherto not understood. It has explained the common cause of subarachnoid hemorrhage and has led to the successful recognition and treatment of many cases of aneurysms which prior to this time were often not even diagnosed. Today, aneurysms are far more common than tumors used to be, and in some clinics more operations are performed for aneurysms than for tumors.

Angiography has also made it possible to recognize various types of vascular lesions that formerly could not be diagnosed during life. With the combination of ventriculography and angiography, it has now become possible not only to locate a lesion accurately, but, in many cases, to predict the type of pathology which will be encountered. This knowledge enables the surgeon to make a more successful approach if he decides to operate, or it may warn him not to attempt any surgery. Striking examples of this are cases of thrombosis of the internal carotid artery, many of which were formerly explored in the belief that the patient had a brain tumor.

Methods for dealing with the problems of focal and general infections of the nervous system made little headway until the discovery of antibiotics. But here again we must not forget the pioneers.[7] The brilliant results obtained without antibiotics in cases of brain abscess by that master, William Macewen,[8] and occasionally by others, should not be forgotten. But, by and large, these infections were a disheartening group.

No consideration of progress in the treatment of brain abscess, however, would be complete without reference to the important work of Clovis Vincent. He advocated decompression over the site of the abscess, thus giving time for the lesion to become encapsulated, and then excising it—a method in very general use today. The untimely death of Vincent deprived neurosurgery of an original thinker who had much to contribute.

The scope of neurological surgery has been greatly extended by a number of other developments, the most important of which has been the use of electroencephalography.[9] This has been a great aid in localizing lesions and has the great advantage that it involves no surgical procedure, but it is not a substitute for either ventriculography or angiography, both of which continue to have a most important place in cerebral localization. Electro-

encephalography has been of particular use in locating a focus not due to an expanding lesion and has made it possible to differentiate the epilepsies and identify those that may be helped by surgery.

Most recently there have been several other developments, some still in the experimental stage, which promise new information and entirely new approaches to problems of both diagnosis and treatment. The first is the use of implanted electrodes for the study of deep-seated areas of the brain and the treatment of mental disorders. A number of clinics are carrying on this work but the most promising, I believe, is that being done by Delgado at Yale. He has devised an apparatus by which he is able to stimulate a number of areas of the brain with one electrode. This method is throwing new light on the functions of deepseated areas which hitherto have been unknown.

An entirely different series of investigations is being carried on with radioisotopes. They are being used both for localization of brain tumors and in the treatment of malignant tumors. This method of approach is so new that it is impossible to draw any conclusions about its ultimate value, but it gives great promise and is being followed with the keenest interest.

Another approach to the problem of malignancy is that first tried by Olivecrona[10] of Stockholm—the complete removal of the hypophysis. The early reports of its effectiveness are most interesting, and here lies another new field for the neurological surgeon. It is important to remember, however, that complete removal of the hypophysis is a much more formidable procedure than the usual pituitary operation.

I have thus far spoken exclusively of the cerebral phases of neurological surgery. Advances in spinal surgery have not been so significant since Victor Horsley[11] removed the first spinal tumor in 1888. But in one phase of spinal surgery—the care of the paraplegic patient—extraordinary advances have been made in recent years. Since the man who, in my opinion, has done more to advance the surgical treatment of this condition than any one else was formerly one of my assistants, I take great pleasure and pride in mentioning him, Dr. Arnold Meirowsky, now of Nashville. In his work in Okinawa, and especially in Korea, he demonstrated how paraplegic patients could be cared for and how the great bugbear, bed sores, could be prevented by appropriate surgery and careful nursing. The record that he and his assistants made in Korea should be an example for every civilian hospital and nursing school to emulate. They proved that the claim—alas too prevalent!—in our civilian nursing schools today that bed sores are inevitable in certain cases is absolutely wrong.

The other great advance in spinal surgery has been the recognition and treatment of ruptured intervertebral discs.[12] First, the lumbar discs were

recognized; more recently, cervical discs are being recognized and treated with equal success. A word of caution is needed here, however, for not all patients with ruptured discs require operation, and it is to be hoped that the excessive enthusiasm for operating upon such cases will subside.

A further great aid is the development of the specialty of anesthesiology. The various methods that have been devised have certainly helped greatly in the handling of difficult cases. Yet, while they have taken a great load off the shoulders of the surgeon, I still am old fashioned enough to believe that if anything goes wrong with the anesthetic, the surgeon is responsible. I realize that this point of view is resented by some anesthetists!

Still another very recent technique that is proving of great value is hypothermia. By lowering the temperature of patients to levels formerly considered dangerous, it is now possible to operate safely on lesions, particularly tumors, that could not be dealt with otherwise. This method is still in its incipiency, but much may be accomplished with it when it is developed further.

Increased intracranial pressure still remains one of our fundamental problems, and the creation of hypotension to overcome this pressure is a recent and important addition to intracranial procedures. There are two ways of applying this, either by removing blood before operation and then reinjecting it, as first suggested by Gardner of Cleveland, or by using drugs. The drugs seem to be more generally used as they can be controlled more accurately.

What a change has come over neurological surgery! Low blood pressure, the very thing we dreaded forty years ago—a common accompaniment of cranial operations which we had no adequate means to correct—is now used by the surgeon as a tool and, what is more, thus allows him to handle cases with which we were unable to cope.

When we consider the amazing advances that have been made, step by step, for the last fifty years, it is little wonder that this field, once so discouraging, should have become so outstanding that it has attracted some of the best minds in surgery. The future looks very promising, and those of you who will be here twenty-five years from now may wonder how the pioneers accomplished what they did and be grateful that, in spite of the great odds against them, they looked to the future and never gave up.

REFERENCES

1. Beevor, C. E. and Horsley, V.: A record of the results obtained by electrical excitation of the so-called motor cortex in an Orang Outang. Phil. Trans. R., 1890, *181*, 129.

2. Cohn, E. J., *et al.*: Chemical, clinical and immunological studies on the products of human plasma fractionation. J. clin. Invest., 1944, *23*, 417-601.

3. Crile, G. W.: *Hemorrhage and transfusion.* New York, Appleton, 1909.
4. Cushing, H.: The control of bleeding in operations for brain tumors. With description of silver "clips." Ann. Surg., 1911, *54*, 1-19.
5. Cushing, H.: *The pituitary body and its disorders.* Philadelphia, J. B. Lippincott, 1912.
6. Cushing, H.: The treatment of tumours of the brain and the indications for operation. Lancet, Lond., 1913, *2*, 552, 739.
7. Cushing, H. and Bovie, W. T.: Electro-surgery as an aid to the removal of intracranial tumors. Surg. Gynec. Obst., 1928, *47*, 751-784.
8. Dandy, W. E.: Ventriculography following the injection of air into the cerebral ventricles. Ann. Surg., 1918, *68*, 5-11; Amer. J. Roentgenol., 1919, *6*, 26-36.
9. Frazier, C. H.: *Trigeminal neuralgia.* Philadelphia M. J. December 1901.
10. Gowers, W. R. and Horsley, V. A.: A case of tumour of the spinal cord. Removal; recovery. Med. Chir. Trans., 1888, *71*, 1-54.
11. Horsley, V. A.: Remarks on the surgery of the central nervous system. Brit. med. J., 1890, *2*, 1286-1292.
12. Horsley, V. A.: The operative treatment of optic neuritis. Ophthalmoscope, 1908, *6*, 658-663.
13. Horsley, V. A.: The function of the socalled motor area of the brain. Linacre Lecture. Brit. med. J., 1909, *2*, 125-132.
14. Jasper, H.: Electroencephalography. Pages 380-454 in: Penfield, W. and Erickson, T. C., Eds. *Epilepsy and cerebral localization.* Springfield, Ill., C. C. Thomas, 1941.
15. Lewisohn, Richard: Clinical results in 200 transfusions of citrated blood. Amer. J. med. Sc., 1919, *157*, 253-271.
16. Macewen, W.: *Pyogenic infective diseases of the brain and spinal cord.* New York, Macmillan, 1893.
17. Mixter, W. J. and Barr, J. S.: Protrusion of the lower lumbar intervertebral disks. N. Engl. J. Med., 1940, *223*, 523-529.
18. Moniz, Egas: *Encephalographie cerebrale.* Paris, Masson, 1934.
19. Olivecrona, H.: Experiences with hypophysectomy in man. J. Neurosurg., 1947, *10*, 301-316.

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SOME THOUGHTS AND AFTERTHOUGHTS ON MEDICAL EDUCATION

Several months ago the State University of New York conducted a Symposium on General Education which was designed as an opportunity for the exchange of ideas among representatives of the many constituent units of the University. In response to a request to present a statement on general education in relation to medical education I prepared a short paper which, I thought, contained a representative aliquot of the educational ideas of the majority of medical school teachers. The predominantly lay audience was politely attentive and many individuals assured me that they had found my remarks interesting and instructive. Since the responses of some of my medical colleagues were rather less than friendly, I have elected to reproduce the paper as it was delivered at the Symposium, together with a brief post-mortem report. These thoughts and afterthoughts seem to me to be particularly appropriate for inclusion in a testimonial volume for John Fulton for reasons which will become very obvious.

General Education As A Preparation For The Study of Medicine

During World War II many research workers devoted all of their efforts to studies on aviation physiology partly because some people believed that objective criteria for pilot selection could be set up on the basis of an understanding of the nature of the physiological stress to which a pilot is subjected. The comparative biochemists, the nutritionists, the endocrinologists, and other special pleaders quickly maneuvered fragments of the problem into their respective areas of study with the result that certain co-ordinators of the program began to be a little mystified. After reading a sheaf of preliminary reports one of them remarked wryly: "It appears from these data that the pilot of the future will be a thyroidectomized turtle maintained on a cabbage and carrot diet."

The paragons our schools and colleges are asked to send to professional colleges in quantity seem to be approximately as widely distributed in nature as are vegetarian thyroidectomized turtles. For, in addition to intelligence and a good appearance, they must have a degree of poise, a hint of approaching maturity, good verbal facility, uncompromisingly high moral and ethical standards, the capacity to work well with people, imagination, enterprise, self reliance, tolerance of the views of others, and a sense of

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humor. Beyond these rather nonspecific attributes, which are required of candidates of all types of professional education from engineering to the ministry, the individual professional college may add a few requirements of its own. For example, some medical school teachers insist on a rudimentary knowledge of arithmetic, chemistry, and physics; others point to the need for instruction in biology; almost all demand of their students the ability to read reasonably rapidly with good comprehension, and some wistfully hope that they will be able to express their thoughts clearly and concisely.

After each of the professional schools has specified its prerequisites, all unite and demand in chorus: give us cultivated gentlemen who know something about the large ideas with which man has been struggling since the beginning of history; about the historical development of ideas as well as of civilizations; about the organization of society and the social and economic forces that shape it; about the literature of the different peoples of the earth, and about their visual arts and music; and, generally, about what Sir Richard Livingston has called "the philosophy of the First Rate."

I submit that, if a first-year class uniformly composed of students of this quality appeared at any medical school in the country, its members would be justified in asking for a tuition rebate on the grounds that each faculty member would doubtless fall somewhat short of combining the best qualities of mind and heart of Louis Pasteur, St. Francis, and Sir William Osler. If we had such able and gifted students, they would probably become excellent doctors if they took their medical course in a correspondence school, and we would all be declared obsolete.

You may be interested to learn that some medical school teachers are almost morbidly preoccupied with liberal education and the humanities at the present time. Perhaps this preoccupation is related to a sort of collective guilt feeling that has been engendered by the frequently heard assertion that doctors have gained technical skills but have lost their hearts in the process. Many recent advances in medicine have been grounded in the physical sciences, and the curricula of medical schools have always stressed the material and palpable aspects of medical care. (Parenthetically, it is unfair to suggest that only the medical profession has been preoccupied with the material and the palpable. In stressing this phase of its development medicine has been reflecting the mood of our whole society.) Furthermore, the rapid development of specialization has fragmented the patient into various parts and orifices at the same time that the increased mobility of our population has markedly inhibited the development of the sort of warm relationship that often existed between a physician and a family thirty years ago.

All of these complex developments have resulted in an equally complex reaction. Possibly the recent re-discovery of psychosomatic medicine was part of the reaction. The constant exhortations to modern medical students to try to "see the patient as a whole" are another part of it. The home care programs in some schools and some of the heroic re-designing of the medical curriculum in others can be traced to some of the developments I have outlined. The attempt on the part of many medical schools consciously to

introduce their students to a social and environmental point of view is certainly causally related to the situation I have described.

It is difficult to assess the rôle which public opinion has played in bringing about the profound change in the philosophy of medical education that has occurred in the past twenty-five years. Gradually, and almost imperceptibly, the medical schools have abandoned the attempt to produce practising physicians in four years. The immense and rapid accumulation of medical knowledge in the past half-century, together with the fear held by certain medical teachers that there is some danger of entrusting the health of our people to the hands of a certain number of empty doctors who have a façade of technical skill, has forced us to reconsider our aims. The evolution of more and more elaborate post-doctoral hospital training programs has been a part of this development. Now, we think of the four-year medical course as a sort of liberal arts course in the medical arts and sciences. Some of us are even optimistic enough to believe that the four-year undergraduate course in medicine has been developing into a varied and ever-changing view of human biology in the largest sense of the phrase. This includes considerations of health and its conservation in addition to the care of the individual sick person. It includes contemplation of those aspects of biology which man shares with other animals, and the ways in which an understanding of the biology of other forms of life helps one to understand human biology. In addition, it includes studies relating to the peculiarly human aspects of human biology up to and including the interphase between medicine and religion. The product of the undergraduate medical course has been described variously as a "non specific" or "undifferentiated" or "ton-potential" physician who will acquire most of his professional skills during the years of hospital training that follow graduation.

If we are indeed moving toward this broad view of the purpose of undergraduate medical education, one can see the relevance to the physician of educational experiences at every step of the educational ladder. I wonder how many primary or secondary school teachers realize how critical a contribution they make to the education of our professional people. Medical education, rather than an end toward which all previous education should be directed, is part of a purposeful collaborative effort of long duration among teachers and students at every developmental stage of the latter. The purpose of this effort is to help a student, through the long voyage of self-discovery, to become a generally educated person who is a physician. This certainly cannot be accomplished by rigid adherence to doctrinaire ideas—even doctrinaire ideas about general education, which seems to be a contradiction in terms. The generally educated physician has, above all, an appreciation of the variety and complexity of human experience, and the humility that derives from such appreciation. This, it seems to me, makes him a better and more effective physician than one whose training has been more circumscribed.

It is unreasonable to ask that every teacher's presentation be enthusiastically received by every student. All students cannot be expected to be equally stirred by every subject or course to which they are exposed. It is reasonable to hope that all students, including pre-medical students, be

exposed to a variety of bodies of information, attitudes, points of view, and, perhaps most important, enthusiasms. Any of these which he accepts and appropriates will be relevant to his later experience.

All sorts of strange and subtle things are happening to our intellectual climate. In the days of Bishop Wilberforce and Thomas Huxley, religion and science were thesis and antithesis. Now nuclear physicists spend a lot of time pondering the problem of good and evil and, indeed, one of them was recently ordained in the ministry. Certain astronomers report their findings with what can only be described as pious awe and write treatises on the limitations of science. Science and art, formerly regarded as mutually exclusive provinces of human endeavour, are coming closer together, for there is high art in creative science. It is, in fact, the aesthetic appeal of science and experiment that attracts certain people to the scientific life. Thus, one cannot differentiate between science and the humanities, for science, in certain of its expressions, is one of the humanities. Finally, medicine itself, which began when a primitive man expressed his concern for a fellow human being in distress by trying to help him, is one of the most humane of the humanities. The fact that interpersonal relations are so very important a part of the practice of medicine makes medicine more of a social science than a precisely quantitative one. This judgment can be made without belittling the vast debt we owe to the physical sciences. In summary, the traditional compartment walls of learning are crumbling and all areas of human knowledge and experience are becoming confluent. Nowhere is this phenomenon seen more vividly than in the field of medicine. That is why we in the medical schools would like our students to come to us with something more than a knowledge of elementary biology, physics, and chemistry, so that each may, in the happy phrase of the motto of this University, become all that he is capable of being.

The response elicited by the paper turned out to be far more entertaining and instructive than the paper itself had been. Quickly it became apparent that an innocent attempt to describe a point of view about medical education to a lay audience was, in fact, a kind of verbal Rorschach test inkblot which, in the minds of certain individuals, became a terrifying collection of spectres, hobgoblins, and Loch Ness monsters.

One disturbed colleague composed a formal rebuttal to the paper. It was the work of an angry man who had been stung into literary action. In his rebuttal he pointed out rather sharply that, after all, medical schools are places where future physicians are taught to care for sick people, and that, when people are sick, they want doctors who understand their illnesses, and they don't much care whether or not their doctors have read Shakespeare. Furthermore, my indignant critic clearly equated the words *general education* with *dilettantism* and, by inference, the phrase *specialization in a narrow field* with *progress* (and, perhaps, even with *profundity*). I have a certain amount of sympathy for these attitudes and, speaking as a recent

patient, I have a vivid appreciation for the urgent necessity of helping medical students to acquire technical and vocational skills. A plea for breadth of training, however, should not be construed as an attack on the scientific and manipulative aspects of medical practice.

Other faculty members, who spend a good deal of their time and energy defending their curriculum time against what they regard as the outrageous assaults of the Psychobiologists, the Environmentalists, and the Sociologists, were frankly disappointed in me because I had, in their view, given aid and comfort to the Enemy by what I had written. This sort of accusation bewilders me, for it implies that quantitative biology and the social sciences are mutually exclusive, and that one's allegiance should be entirely to one or the other. The patent absurdity of this proposition does not prevent this contrived controversy from occupying much of the time of many medical school curriculum committees.

One of my friends asked me in horror whether I seriously believe that religion should be taught in nonsectarian medical schools. I replied that certain medical schools have abandoned the pretense that religion does not exist by arranging discussions of the religion-medicine interphase for the benefit of those students who elected to hear them. We sponsored such discussions in our school as part of a First Year Orientation Course and the students found them both stimulating and instructive. It was generally believed that the individual student felt especially rewarded as a result of hearing discussions of these matters by representatives of faiths other than the one with which he was most familiar.

Finally, largely as a result of many hours spent on various medical school committees, I began to have some disturbing afterthoughts about my own essay. Through a dim montage of recurrent themes endlessly discussed qualifications for admission, interview evaluation, examinations and grades, opportunities for elective work, internship and career advice I began to see that there are elements of serious misrepresentation in the advice we give pre-medical students and their advisers. Most of us advise undergraduates to prepare for medical school by taking as much work in the humanities as they can get. Many medical school faculty members who serve on admissions committees reward the humanities majors by being elaborately disinterested in their achievements in the humanities, since these achievements are not generally conceded to have a high predictive value for academic performance in medical school. Most admissions committees want to know how well the candidate performed in organic chemistry. Since these are the grim facts of life at the present time, are we being quite candid when we tell pre-medical students that we want well-rounded men who do lots of interesting extracurricular things in college? Possibly we

should be telling them to become well rounded and extracurricular only after they have successfully demonstrated their competence in organic chemistry.

Most of our medical schools are examination and grade-centered and many of them have rather rigid curricular structures. The academic pressures are so high that it is often impossible for a student to continue an undergraduate interest in medical school if it is not specifically related to the course of study. Furthermore, some of our ex-humanities majors tell us that they never quite recover from the shock of adjusting to the first-year medical school curriculum. (Of course, this is also true of some ex-science majors). Is it not true that basic science instruction in most medical schools qualitatively resembles science instruction in the colleges much more closely than it does collegiate instruction in philosophy, literature, or political science, and that a science major might be expected to enjoy a competitive advantage in the basic science years? The melancholy fact is that there is little opportunity for discovering the special skills, interests, and aptitudes of individual students in most of our medical schools. Where such opportunities exist (at Yale, for example) many students acquit themselves admirably. One can only hope to see a gradual disappearance of the compulsive type of curriculum planning which imprisons both student and faculty in rigid and arbitrary relationships.

Have these confessions come to a full circle? Do the afterthoughts neatly cancel out the thoughts, and are we, therefore, left with a commentary on a set of asthenic clichés? Possibly. But it seems to me that the undergraduate colleges and the medical colleges can do much to create an environment for learning in which the study of medicine can be something more than the acquisition of readily negotiable information, for we are being subjected to formidable "anti-egghead" pressures from many of our colleagues as well as from our students.

Traditionally, medicine has been in the main stream of our cultural heritage. We owe an enormous debt to men like John Fulton, who have demonstrated that the cultural traditions of medicine can be preserved and strengthened while the scientific basis of medicine is enlarged and enriched.

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THE TERMINAL ARBORISATION OF THE CAT'S PYRAMIDAL TRACT DETERMINED BY A NEW TECHNIQUE[¶]

As neurophysiologists move away from topics of gross organization toward an interest in the finer details of cellular arrangement, it becomes necessary to describe the microscopic distribution of terminal fibers. Gross anatomical methods such as that of Marchi degeneration provide information only about gross connectivity, e.g., that a particular tract loses its myelin in a certain region and therefore probably terminates there. The beautiful Golgi technique tests the extremes of skill and patience of the anatomist. It is particularly difficult to use where the endings of long axons are being examined since the cell body of the axon cannot be seen and the exact origin of an axon cannot be known. However, such workers as Ramón y Cajal, Lorente de Nó, and Sholl have proved the extreme usefulness of the Golgi method. The recent modifications of the Bielschowsky technique by Nauta and Glees have revived interest in the degeneration method of finding endings. The future of this method seems hopeful but there are marked difficulties in technique and interpretation, particularly because of different results obtained by divers workers.

It is also possible to use the conductive properties of nervous tissue to map connections. On the gross level of the Marchi method we have neurography by strychnine and stimulation, the finding of evoked responses with minimum latency, etc. These tricks are useful for rapid plotting of rough connectivity but also produce their own special problems, some of which are mentioned in another paper.[6]

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Until recently we have had no electrical technique comparable to silver stains because it is difficult to decide what is relevant signal. The interpretation of slow potentials arising in regions of synapsis is most ambiguous—indeed it forms the battleground of opposing theories of synaptic transmission. How such potentials are related to their generators within the signal cord is discussed in another paper.[5] Obviously it would be foolhardy to attempt a fine resolution of detail in the presence of such considerable mixing and smearing of signals as occurs under orthodromic stimulation. However, in our work we discovered that it was possible to excite very locally the terminal fibers and record with little decrement the antidromic impulses as digital events in the parent axons.

We describe here results obtained by recording the antidromic volleys generated in terminal arborisations by microelectrode stimulation. By locating each of the large number of stimulation points, we build up a map of the distribution of the endings. The resolution of the method stands between the best anatomical methods and the Marchi technique and is greatly superior to previous physiological methods. It has the advantage of speed and simplicity and can be applied to finding the distribution of endings from a very small number of fibers.

EXPERIMENTAL TECHNIQUE

The microelectrodes used in these experiments were cylindrical and made of glass-covered platinum wire. The length of the cylindrical thin part was about 5 mm. Two types were used—monopolar electrodes, containing 10-micron platinum wire with an over-all diameter of about 20 microns, ground to a point at their ends, and bipolar electrodes, containing two separate 10-micron platinum wires, with an over-all diameter of 50 microns or less. In the latter type, the tip was ground so that one wire was exactly at the tip and the other emerged on the bevel about 10 microns behind the leading wire. The method of manufacturing these types of electrodes is described elsewhere,[6] as is also the method of localizing the electrodes.[7] Briefly, the electrodes are pushed into the nerve tissue under the control of a micrometer. The entry is observed under a microscope and the presumed depth of penetration is read off the micrometer. At the maximum depth attained by the electrode, it is cut across with fine scissors and left in place. The cutting is done under the microscope and produces little change in the position of the electrode. At the end of the experiment the tissue is fixed *in situ*; a slab containing the electrodes is cut out, dehydrated and finally cleared in methyl salicylate. A photograph is then taken of the section and the position and depth of penetration of the electrodes is determined. Only those electrodes whose actual depth in section and presumed depth from the micrometer reading agree to within five per cent are used for plotting results. The electrodes used have a complex impedance in which both the resistance and the reactance vary as the minus 0.95 power of the frequency. When the frequency is above 5 kc, the electrode resistance is lower than the tissue resistance. The stimulator used generated constant-current pulses about 0.2 msec. long.

The current flowing from the tip of the electrode was adjustable from 0.1 to 50 μa but was usually kept at about 0.5 to 5 μa. Since even light barbituate anesthesia increases the threshold of terminal afferent fibers, the experiments were carried out wherever possible in spinal or decerebrate cats. Evoked motor movement was controlled either by curare or by ventral root section. The segments of the spinal cord to be examined were exposed by the usual laminectomy and covered with oil. The temperature of the animal and of the bathing oil was controlled throughout the experiment.

EXPERIMENTAL RESULTS

1. *Localization of large, sensory nerve fiber endings and motor horn cells in the grey matter of the lumbar cord.* In this set of experiments the accuracy of the localization of the stimulus was first tested by stimulating motor horn cells. In the right-hand diagram of Figure 1 the results are shown. Recording electrodes were placed on the cut ventral root of the first sacral segment. Stimulating microelectrodes were lowered into the spinal cord. The black dots show the points from which direct responses on the ventral root were evoked by direct stimulation of the motor horn cells. The dotted line represents the extreme of penetration of the electrodes in this experiment. Of course, responses occurred in the ventral root when many other parts of the cord were stimulated but these were delayed by more than a millisecond after the stimulus, implying synaptically evoked activity of the motor horn cells. It is clear from the distribution of responsive points, first, that the resolution is quite good since no responses were evoked by stimulation in the white matter immediately adjacent to the ventral horn and, second, that dendrites were not being stimulated. The distribution shown is, as histologists agree, that of the motor cell bodies and axons. We know from other experiments that the point of stimulation on these cells has a threshold which is modified by the arrival of afferent nerve volleys. This modification of excitability differs if anodal, rather than cathodal, stimulating pulses are sent through the monopolar type of microelectrode. It seems likely, therefore, that different parts of the cell are being stimulated, depending on the sign of the stimulating current. Impulses were generated in the terminals of afferent fibers, at the same time as in the motor horn cells, and passed antidromically out the dorsal roots. Presently, a large number of studies on the endings of sensory fibers from various peripheral nerves in the grey matter of the cord have been done. Here, however, we wish to show only one example.

In a number of cats the lumbar enlargement was exposed and all lumbar and sacral ventral roots on one side were cut. Next, the nerves to the gastrocnemius were dissected out, cut, and placed on recording electrodes. A series of microelectrodes were lowered into the cord and, at 100 micron

intervals during the descent of each one into the cord, a stimulus was given. If a response on the peripheral nerve of gastrocnemius occurred within 1.4 milliseconds, it was taken as an indication that intraspinal fibers belonging to the large (group I) sensory fibers from the gastrocnemius nerve were present close to the tip of the stimulating microelectrode. Since all the motor roots had been cut, there was no chance of confusion between the motor and sensory components of the nerve. We see in the left-hand diagram of Figure 1 the deep penetration of these fibers into the ventral horn. This distribution of sensory-fiber endings contrasted markedly with the slower conducting sensory fibers which terminated in a band across the ventral part of the dorsal column or the slowest conducting fibers which terminated in the substantia gelatenosa. The threshold of the endings of the group I fibers in the ventral horn was surprisingly low, being about the same as that of the motor horn cells.

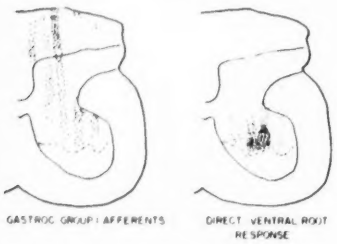

FIG. 1. *Left:* distribution of group I fibers from the nerve to gastrocnemius in the grey matter of the first sacral segment of the cord; determined by multiple microelectrode placements for stimulation and recordings taken from the peripheral nerve after sectioning of motor roots. *Right:* distribution of points from which direct stimulation of motor horn cells was obtained; dotted lines represent the deepest penetration limit of the microelectrodes so that no data were collected from the area ventral to this line.

2. Localization of the endings of the pyramidal tract in the spinal cord. Recordings were taken from the pyramidal tract 2 mm. behind the pontomedullary junction. The most useful type of recording bipolar electrode was an insulated nichrome wire in a hypodermic needle tube (27 gauge). The end was shaped to a point by setting it in Stycast plastic resin and grinding it down to the required shape after polymerisation. The electrode was lowered into position either by Horsley Clarke coordinates or more simply by removing some of the posterior midline cerebellum and inserting the electrode 1 mm. lateral to the visible midline of the floor of the fourth ventricle. The position of the electrode was checked at the beginning of the experiment by stimulation of the motor cortex before decerebration and at the end of the experiment by histological examination. Next, the cervical enlargement was exposed and microelectrodes were lowered one after the other into the cord. A stimulus was delivered through the microelectrode at each stage of the penetration until the more ventral parts of the cord were reached, after which the electrode was cut off and left in place for later localization. Figure 2 shows the distribu-

tion of the electrode positions in the grey and white matter which produced a response in the pyramidal-tract recording electrode in the medulla. This is one of seven experiments in cats, all of which showed essentially similar results. In this experiment nine electrodes were used; the three most medial ones failed to evoke any antidromic volleys in the pyramidal tract, while the six more lateral ones evoked responses in the area indicated in the figure. In this and in the other experiments very minor responses were found from a slightly more extensive area although never extending into the ventral horn. The responses recorded in the marked area were definite even at the edges and increased in size rapidly as the electrode was moved toward the center of the marked area. The edge of the area was remarkably sharp, both with bipolar electrodes and with monopolar electrodes, provided the current flow was controlled. The simplest way of checking the extent of current spread was to place the stimulating electrode just to one side of the midline in the dorsal columns and check on relevant dorsal roots - for spread of the stimulus across the midline to the contralateral dorsal column. In this way, it was possible to maintain a small area of stimulus even with monopolar electrodes. The monopolar electrodes had two advantages, first, greater ease of manufacture than the bipolars and, second, the interesting finding that they were far more efficient in stimulating white matter, presumably because the bipolars failed to stimulate many myelinated fibers because of the absence of nearby nodes.

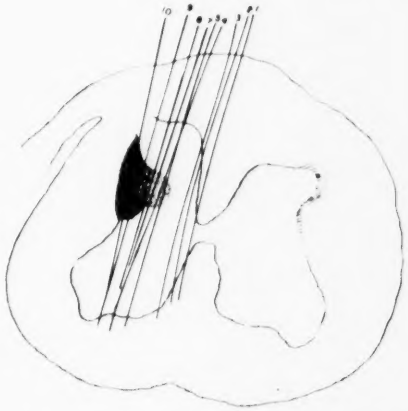

FIG. 2 Distribution of points in a lower cervical segment of cat spinal cord from which microelectrodes could elicit antidromically-traveling impulses recorded in the medullary pyramid. This shows the extremely limited extent of the penetration of the terminal arborisation of the pyramidal tract into the spinal cord grey matter. Conduction speed of the antidromic impulses about 65 m/sec.

Three facts should be noted. First, the area in which the pyramidal tract appears to end does not extend into the ventral or extensively into the dorsal horns. Second, it was not possible to demonstrate the presence of a

direct pyramidal tract in the lower end of the cervical region of the cat although this may have been caused by the localizing nature of the pick-up electrode in the medullary pyramids. Last, there were no clear signs of projections into the pyramidal tract of ascending direct sensory fibers. This does not mean that no other waves were recorded from the electrode in the pyramidal tract but it was clear from their size, timing, and maximum, determined by moving the electrode, that these were impulses traveling in the adjacent medial lemniscus and other white matter. No signs of pyramidal projection into the lumbar enlargement could be found in the cat. In one rhesus monkey the terminations of the pyramidal tract in the cervical enlargement were again found to be similar to that in the cat with no signs of projection onto the ventral horn cells. The distribution of endings in the monkey extended slightly more ventrally and medially into the intermediate grey than in the cat.

DISCUSSION

Our technique involves the penetration of a series of microelectrodes into the area to be searched. We have placed up to fifteen monopolar electrodes in a half cross-section of the spinal cord without being able to detect any change in the reflex pattern involving that segment of the spinal cord. It is evident, therefore, that the damage produced by the electrodes does not severely upset the intraspinal organization. As a further check against damage, we have frequently inserted the final electrode of an experiment into the middle row inserted during the previous few hours. The results obtained from this interpolated electrode are consistent with the pattern established by its neighbors so that there are no signs of progressive damage. Rarely, a change was seen during an experiment and on examining the cord later we have found a small petechial hemorrhage surrounding one of the electrodes. However, this is so rare that it is clear that the collision of the electrodes with blood vessels does not usually result in bleeding.

With monopolar electrodes, and to a lesser extent with bipolar electrodes, it is obvious that if the current strength is high enough, distant parts of the nervous system may be stimulated. As we mentioned above, the current strength was controlled to obtain the optimum resolution. If there existed within the spinal cord gross inhomogeneities of electrical resistance, the use of a fixed stimulating current might give spurious localization of responding points. We have examined this by mapping the current distribution within the cord from a single point source. While it is true that there is a difference in resistance between the white and grey matter, this in-

homogeneity does not significantly distort the localization of terminals which we describe in this paper.

On looking at the very short distance of penetration of corticospinal fibers into the dorsolateral grey the question may be asked: "How sure are we of stimulating the collaterals all the way to their terminals?" Not only have we the results of tracing the dorsal root afferents all the way to the ventral horn, but we have mapped *pari passu* with the pyramidal fibers the distribution of the medial longitudinal fasciculus. The latter gives rise to very long collaterals ascending from the ventral columns to the very edge of the dorsal columns; the method of recoding in the brainstem was exactly the same as that used for the pyramids.

Thus, for the cat, we have definitely confirmed the impression of others that the intraspinal fibers of the pyramidal tract end in the deeper part of the dorsal horn and extend slightly into the intermediate region. No signs of invasion of the ventral horn could be seen. This agrees with the anatomical findings of Rasdolsky[5] and the physiological findings of Lloyd.[6] We were unable to find any signs of ascending sensory fibers within the pyramidal tract as reported by Brodal and Walberg,[7] and by Brodal and Kaada.[8] In all experiments signs of ascending sensory volleys were seen but on more careful localization they were found to be running in tracts dorsal to the medullary pyramids.

Unfortunately, we cannot make as definite a statement on the endings in the rhesus monkey. Hoff and Hoff[9] reported anatomical studies showing a few scattered endings of the pyramidal tract in the ventral horn. Bernhard, Bohm, and Petersen[10] have recently reported monosynaptic facilitation of the motor neurons in the monkey. It is evident from their writings that they had some difficulty in evoking this monosynaptic effect and it seems usually to have been necessary to send long bursts of impulses down the pyramidal tract from the cortex before the effect could be seen. In the one experiment we have been able to carry out in the monkey, it is true that the area containing endings extended more ventrally and extensively into the intermediate region than in any of the cats examined. However, the area did not include the ventral horn segments in which Hoff and Hoff[9] show endings and could at best have connected with some long meandering dorsal dendrites of some motor horn cells. Thus, while it is clear that the pyramidal tract in the monkey is far more developed than in the cat, especially in its invasion of lumbar segments, we have not been able to confirm that its intraspinal organization is radically different from that of the cat, although this point requires further investigation.

SUMMARY

1. A new technique is described which uses antidromic impulses generated in terminal arborisations by stimulating microelectrodes. The position of the stimulating microelectrode is determined for those points of stimulus which evoked a response recorded in a tract projecting into the stimulated area. The resolution of the technique is shown to be greatly superior to previous physiological methods which attempted to localize the ending of projection fibers.

2. The technique is used to show the endings of the group I afferent fibers from the gastrocnemius muscle in the grey matter of the cord.

3. The ending of the pyramidal tract in the cat is shown to be limited to a small region in the ventral part of the dorsal horn. Preliminary results on the monkey are also discussed.

REFERENCES

1. Bernhard, C. G., Bohm, E., and Petersen, I.: Organization of the corticospinal system in monkeys. Acta physiol. scand., 1953, *29*, 79.
2. Brodal, A. and Kaada, B. R.: Exteroceptive and proprioceptive ascending impulses in the pyramidal tract of cat. J. Neurophysiol., 1954, *16*, 567.
3. Brodal, A. and Walberg, F.: Ascending fibres in the pyramidal tract of cats. Arch. Neurol. Psychiat. (Chicago), 1952, *68*, 755.
4. Hoff, E. C. and Hoff, H. E.: Spinal terminations of projection fibres from the motor cortex of primates. Brain, 1934, *57*, 454.
5. Howland, B., Lettvin, J. Y., McCulloch, W. S., Pitts, W. H., and Wall, P. D.: Reflex inhibition by dorsal root interaction. J. Neurophysiol., 1955, *18*, 1.
6. Lettvin, J. Y., McCulloch, W. S., Pitts, W. H., and Wall, P. D.: Some effects of strychnine. Epilepsia, 1955, in press.
7. Lloyd, D. P. C.: The spinal mechanism of the pyramidal system in cats. J. Neurophysiol., 1941, *4*, 525.
8. Rasdolsky, J.: Über die endigung der extraspinalen bewegungssysteme. Z. ges. Neurol. Psychiat., 1923, *86*, 361.

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SYMBOLIC ASPECTS OF THALAMIC PAIN

Pain associated with hemiplegia has been considered mainly in the context of the thalamic syndrome. Since the original observations by Dejerine[1] and Roussy,[2] many cases have been reported and all textbooks of neurology carry a description of it. The cardinal points have been the presence, on the side opposite the lesion, of spontaneous pain and an over reaction to sensory stimuli. Most of the cases have included a loss or reduction of perception of touch, pin prick, thermal, and proprioceptive modalities, but Head[3] pointed out that this diminution may be extremely slight and discoverable only by finer methods of examination.

Despite its establishment as a classical entity and the ease of diagnosis, a number of puzzling features remain. First there is the paradox of an over-reaction to stimuli in an area of diminished sensibility. Roussy localized the syndrome to a lesion in the lateral thalamic nucleus on the basis of autopsy studies, and French neurologists, in general, have attributed the hyper-reaction to irritation of the thalamic paths. Head considered that this feature was the result of the release of control of higher, i.e., cortical, centers. The specificity of the syndrome as "thalamic" has been questioned by the quoting of cases with central pain in more cephalad lesions.[4-6] Further, it is a fact that most patients with hemiplegia and lesions involving the thalamus or cortico-thalamic pathway do not complain of pain in the affected extremities.

Although a clinical entity, the thalamic syndrome is of neurophysiological interest because until comparatively recently our knowledge of the thalamus and its functions was based on such clinical and histological studies. The present paper is a reinterpretation on the basis of recent work on the organization of the thalamic nuclei, particularly in reference to the non-specific projection systems, and to the development of understanding of such alterations in symbolic organization of perceptual modalities as anosognosia, inattention, and pain asymbolia.

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OBSERVATIONS

Five patients with pain on the affected side of the body were encountered in a study of the behavioral changes of 108 patients with hemiplegia due to vascular and neoplastic disease. All had characteristics of the thalamic syndrome in some degree and will be described from the standpoints of the following: (i) character of the pain; (ii) findings on sensory examination; (iii) other alterations in behavior; and (iv) relation to the premorbid personality.

The pain involved mainly the extremities and to a lesser degree the face on the side of the painful, paretic limbs. It was described as "terrible," "awful," "something tearing me apart," "as if it's grabbing me in a vise," and "one thousand needles pricking me." In three of the patients sensations of "coldness," "numbness," and "deadness" were also described. Mention of the pain was frequently accompanied by grimaces and groans. In the hospital the complaints of pain were more marked when the doctor approached the patient's bed. An exacerbation might be produced by an examiner's touching, picking up, or even talking about the affected limbs. Yet on occasion the limb might be handled without causing pain. Some patients were turned and dressed by nurses without pain. One man would rub his leg while talking about the pain in it, a maneuver which if performed by the examiner usually produced pain.

The sensory examination during the acute stage in all patients revealed a midline demarcation in which the perception of all modalities was lost or reduced on the affected side. This included not only stereognosis, two-point discrimination, and the sense of passive motion in the hand, but touch, pin prick, temperature, and vibration. In two cases with vascular disease the sensory status improved and comparatively little deficit was found by the ordinary method of examination. In these patients when stimuli were simultaneously applied to homologous parts of the body, only the stimulus on the healthy side was perceived (extinction). In another patient pain persisted even after sensation, when tested by double simultaneous stimulation, had returned to normal. In three patients the complaints of pain did not come on for several weeks after the initial ictus, and in all it has persisted for the periods of observation (two months to three years).

The patients were usually depressed and talked about little except their pain. In one man the depression was interspersed with short spells of euphoria while paranoid attitudes were common. In the patients in whom pain came on later in the illness, there was an initial stage when they were disoriented, incontinent, and expressed various delusions. There seemed to be an inverse relationship between the existence of such phenomena and

pain. None of these patients showed such forms of symbolic adaptation as anosognosia (denial of hemiplegia) or a well-marked inattention to or "unawareness" of the paralyzed side (autotopagnosia).

An account of the premorbid personality was obtained in four cases. These descriptions by relatives were colored by the informants' own motivations but they were significant in indicating the nature of the family relationships. All were considered to have been emotional, excitable, worrying people, quite dependent on the attitudes and actions of others. Three were characterized as hypochondriacal, reacting to stress with physical symptoms and temper outbursts. The dependence was described in terms of wanting attention and physical care, in the demanding of affection, in attitudes about food. The members of their families seemed to relate to one another in material ways, in terms of physical affection and violence, in vocal rather than verbal expressions. The following case report of the patient in whom pain seemed the most severe is illustrative of the social background.

CASE REPORT

A 48-year-old factory worker was admitted to The Mount Sinai Hospital on December 2, 1952, two weeks after the sudden onset of a left hemiplegia. A year previously he had been hospitalized for coronary thrombosis. Examination showed a moderately severe left hemiparesis. There was astereognosis in the left hand and loss of position sense in the left fingers and toes. There was also a marked diminution in response to touch, pin prick, temperature, and vibratory stimuli over the entire left side of the body with a sharp midline demarcation. The patient was able to distinguish the sharp point from the dull end of a pin but felt no pain even on vigorous application over the left side. Visual fields were intact when an object was presented singly on either side but when shown simultaneously he perceived only the one on the right. He was disoriented for time of day, confusing morning and afternoon. Lumbar puncture yielded a clear fluid under normal pressure with a total protein content of 59 mg./100 ml. EEG record showed one to three per second activity over the right-sided electrodes and some diffuse bilateral four to five per second activity.

Throughout his hospital stay of two weeks the patient was depressed and delusional. He expressed awareness of his disability and became completely oriented for time but tended to ignore his left limbs and moved them very little. He stated that the patient in the next bed had been an experimenter in a Nazi concentration camp. He frequently asked why God had punished him. He wanted to be forgiven by a friend of his son whom he had scolded on the day before his stroke. He felt that the nurses were trying to harm him and was delusional about electric wires on his head.

At home the delusions continued for another week. As they cleared, the patient seemed tense and restless and complained of numbness in his left leg. This was followed in two weeks by a complaint of pains and coldness over his entire left side, particularly in his leg. Neurological examination on March 1st showed a slight weakness and clumsiness of the left limbs with no demonstrable sensory loss. He complained

of pain when slight pressure was applied and said that pin pricks had a disagreeable burning quality. He had an appearance of suffering and described his pain as "grabbing" and "tearing me apart."

During the subsequent 18 months the patient obtained no relief from his pain despite various medications. In interviews he presented little ideation apart from the pain and conceived of his disability and personal problems entirely in terms of the pain. He also complained of irritability, lethargy and insomnia, but felt that these were caused by his pain. In October, 1954, he was re-admitted to the hospital. He was given a course of scopolamine and during a period when he became confused and sleepy he complained less of pain. After receiving an electroshock convulsion for treatment of his depression he died.

An account of the family background was obtained in a series of interviews with the patient's wife and two sons. He was described as having been an excitable, worrying person, easily aggravated and possessing a violent temper. He had been ailing for many years prior to his heart attack, particularly with complaints about his stomach. His dependence on his wife was shown by his refusal to go to bed without her, an insistence that she make the appointments and go to doctors with him, and a dislike of all food that she hadn't cooked. With the members of the family he was demanding and critical but appeared self conscious with and afraid of outsiders. In talking of her husband, the wife interspersed many of her own complaints, particularly an "ulcerated stomach" which she stated had come from worrying about the patient. Both attributed the patient's stroke to concern over the delinquencies of his younger son. The parents and this son had commonly exchanged feelings by striking, cursing, and the use of such expressions as "drop dead."

DISCUSSION

The observations suggest that in these patients both the pain and the pattern of the more objective sensory findings may be considered as symbolic manifestations rather than as specific perceptual or physiological entities. It is significant that attempts to delineate discrete, physiologically measurable mechanisms in these patients, such as pain thresholds and vasomotor responses,[7] have not succeeded in demonstrating differences on the two sides of the body. The loss of sensation and the hypersensitivity are not opposite and contradictory phenomena in the sense that one is due to a defect and the other caused by "irritation" or "release," but both are forms of conceptualization or language. The pain, the reported sensations of coldness and deadness, and the apparent absence on sensory examination of feelings on the affected side are all the product of an integration, on a symbolic level, of much more undifferentiated perceptual elements. What the

patient experiences is the conceptualization of these in terms of his own interaction in the environment, particularly in relation to the stressful situation brought about by illness and disability. In this light one can appreciate more fully not only the description of pain as a form of applied torture, but such remarks as those of Head's patient whose right side "craved for sympathy" and whose hand "wanted to be placed on the soft skin of a woman." Usually not only the affected limbs but the whole half of the body is so conceptualized; another patient of Head's complained that even her stomach worked painfully on the affected side.

The necropsy reports in cases of thalamic syndrome indicate that the pathology extends far beyond the limits of the specific thalamic relay nuclei and in all likelihood involves the diffuse projection systems bilaterally. This type of neural involvement is also found with other symbolic patterns such as anosognosia, inattention to the hemiparetic side of the body, pain asymbolia, and akinetic mutism. In patients in whom these phenomena are well developed, pain is inconspicuous. In the case reported in detail the patient while he was delusional did not complain of pain, suggesting that these forms of symbolic interaction are to some extent reciprocal. Previous studies have shown that none of these forms of symbolic interaction is attributable to a specific deficit in any discrete motor, sensory, or mnestic element.[7] Rather there is an alteration in the mode of interaction in the environment in which the patient to a far greater degree selectively expresses his motivations in terms of its spatial, temporal, personal, and somatic aspects. Whether this is expressed as a denial of the paralysis, as inattention to the affected side or in terms of pain, seems to be closely related to the type of premorbid personality and the consequent nature of interpersonal relationships.

The importance of this predisposition to the use of pain as a means of symbolizing social relationships is illustrated by the fact that pain in lesions of the nervous system is notoriously resistant to neurosurgical remedies. In this respect pain in hemiplegia may be compared with the painful phantom limb. While phantoms following amputation are almost universal, the painful phantom is not. In a study of amputees from the Korean war, Price[8] found that even the nonpainful phantom is not felt as a normal limb but that there is inevitably some type of paresthesia. Rather than considering the nonpainful phantom as normal and "physiological" and the painful limb as "psychological," Price believes that all the sensations reported were in some degree conceptualizations of social relationships. One of our patients was a soldier who had had an amputation of the left arm after his axillary artery had been severed by a machine gun bullet. After the painful phantom had not yielded to drugs and minor surgical procedures, a right mesencephalic

tractotomy was performed. Following this operation he complained of pain over the entire left side and was hyperesthetic to stimuli when examined and a subsequent lobotomy similarly failed to relieve his pain.

The paper has presented some clinical observations which suggest that the thalamic syndrome cannot be understood as the result of the interruption or the irritation of specific sensory pathways or as the manifestation of a concept as "release." Nor should it be regarded as "psychological" in the sense that it appears apart from an altered milieu of brain function. It is hoped that further knowledge of the relationships of diffuse and discrete projection systems and studies of the dynamics of interpersonal relationships will give clues as to the manner in which perceptual and motor elements are integrated into conceptual patterns.

SUMMARY

Observations of five patients with pain associated with hemiplegia are presented with particular reference to thalamic syndrome. It is suggested that the syndrome is not explicable on the basis of an interruption or irritation of a specific sensory pathway or in terms of the concept of "release of inhibition" but is a manifestation of an integration of neural function at a symbolic level.

REFERENCES

1. Critchley, M.: *The parietal lobes*. London, Edward Arnold & Co., 1953.
2. Davison, C. and Schick, W.: Spontaneous pain and other sensory disturbances. Arch. Neurol. Psychiat. (Chicago), 1935, *34*, 1204.
3. Dejerine, J. and Egger, M.: Contribution à l'étude de la physiologie pathologique de l'incoordination motrice. Rev. Neurol., 1903, *11*, 397.
4. Dejerine, J. and Roussy, G.: Le syndrome thalamique. Rev. Neurol., 1906, *14*, 521.
5. Head, H.: *Studies in neurology*. London, Hodder and Stoughton, 1920.
6. Marquis, D. G. and Williams, D. J.: The central pathway of the vasomotor response to pain. Brain, 1938, *61*, 203.
7. Price, D.: Personal communication.
8. Weinstein, E. A. and Kahn, R. L.: *Denial of illness, symbolic and physiological aspects*. Springfield, Illinois, C. C. Thomas, 1955.
9. Weinstein, E. A., Kahn, R. L., and Slote, W.: Withdrawal, inattention and pain asymbolia. Arch. Neurol. Psychiat. (Chicago), 1955, *74*, 235.

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SYNCHRONIZATION OF INSPIRATORY MOTOR ACTIVITY AS COMPARED BETWEEN PHRENIC AND VAGUS NERVE

Motor synchronization is known to occur in the phrenic nerve of rabbit, cat, and dog.[1-3] It only develops with reinforced inspiratory activity, such as dyspnoea, whereas with quiet, eupnoeic breathing the inspiratory impulses remain asynchronous.[2,3] Synchronization does not appear even with strongest reflex tonus of inspiratory muscles and therefore seems to depend on some kind of centrally induced, spontaneous activity.[2,3] Its central origin is also demonstrated by the dependence of the frequency of the synchronized efferent volleys on central temperature and by direct recording of a similar rhythmic activity from the caudal part of nucleus ambiguus.[4] The latter findings, however, do not provide any further evidence concerning localization of the source of synchronized activity because they are merely concerned with the outflow at the motoneuronic level of the vagus and particularly the inferior laryngeal nerve.

Synchronization of inspiratory neurons seems to occur simultaneously in the various motor nuclei of inspiratory muscles. This was shown for one phrenic nerve and the opposite side of the diaphragm[1] and may also be deduced from comparison between one phrenic nerve and the ipsilateral or contralateral vagus or inferior laryngeal nerve.[2] Experimental data, however, were obtained from records taken at a relatively low speed and with asymmetrical amplifiers, and may therefore not allow definite conclusions to be drawn concerning identity of frequency and phase relation prevailing between the synchronized activity of different and widely separate pools of inspiratory motoneurons. Since the problem is of great importance with regard to further study of the spontaneous activity of inspiratory centres, the present investigations were undertaken in order to provide more reliable experimental evidence as to the existence of a common pace making mechanism responsible for synchronized inspiratory innervation in phrenic and vagal outflow.

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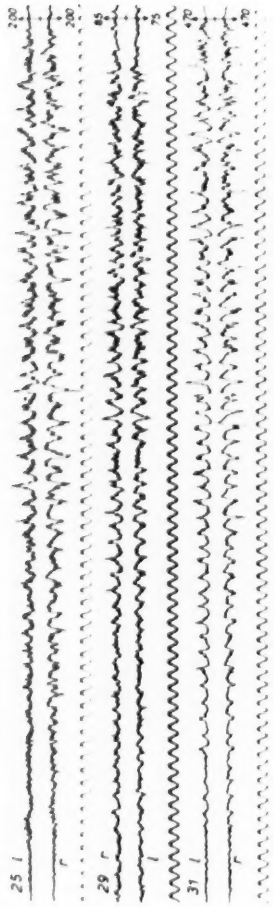

FIG. 1

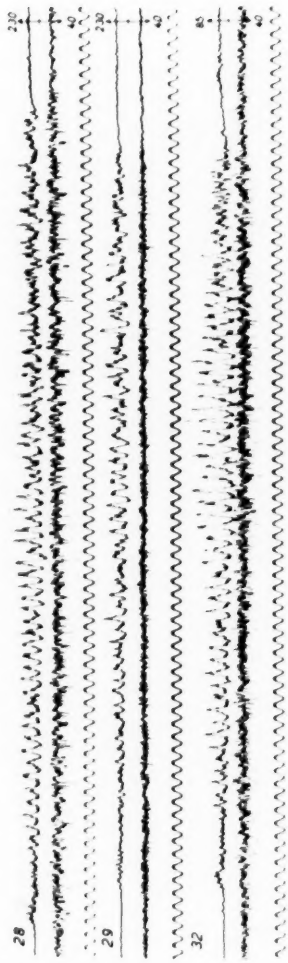

FIG. 2

FIG. 1. Comparison between the two phrenic nerves (R, L) of synchronized activity obtained during early stage of severe dyspnoea. Complete inspiration period from three different experiments, as numbered on the left. For particulars, see Table I. Time marker: 100 per second; to be read from left to right. Ordinate calibration in microvolts, arrows indicate negativity of proximal electrode.

FIG. 2. Comparison of inspiratory activity between phrenic nerve (above) and vagus nerve (below) during early stage of severe dyspnoea. Complete inspiration period from three different experiments, as numbered on the left. Note phrenic synchronization against asynchronous activity in the vagus. For particulars, see Table I. Time marker: 100 per second, from left to right. Ordinate calibration in microvolts; arrows indicate negativity of proximal electrode.

METHODS

Twenty-eight rabbits were used anesthetized with Urethane (1.0 g. per kg. body weight) given *per rectum* as a 25 per cent solution. All animals were tracheotomized and vagotomized bilaterally. They were subjected to artificial respiration in those cases in which the chest was opened or both phrenic nerves were cut, or in which hyperventilation was necessary in order to induce apnoea; all the other animals breathed spontaneously.

One or both phrenic nerves were prepared low in the neck. The main branch was freed from brachial plexus, severed distally, and drawn into a small tubular electrode of 2 mm. inner diameter, 8 mm. length, and containing two chlorinated silver rings at 3 mm. inter-electrode distance. One or both vagus nerves were prepared high in the neck and sectioned at 20 mm. central length. This central stump was introduced into a wide ampullaceous glass electrode of 4 mm. inner diameter, 25 mm. length, in which two axial silver rings were fixed at 15 mm. inter-electrode distance. The nerve was thus kept free from contact with the inner wall of the electrode and action currents could be recorded at maximum amplitude. The three or four electrodes were carefully closed and insulated at the distal end, adequately placed in the depth of the neck and completely covered by attaching the skin from both sides over the midline. This procedure ensured high consistency of recordings and proved to be as satisfactory as the common mineral oil technique.

Electrical recording was accomplished by means of two symmetrical amplifiers[7] on a double-beam cathode-ray tube (*Diamant* 5 SP). The all-over frequency response was limited so as to be flat between 20 and 2000 per second. Maximum sensitivity was 4 cm. per 100 microvolt as measured on screen of tube. Photographic recording was obtained with Zeiss Tessar 1: 4.5 on continuously moving bromide paper 6 cm. in width, at linear speed between 2.3 and 6.7 cm. per second with electromagnetic time-marker controlled by the mains (50 cycle a.c.). For higher speed paper moved at 43 or 89 cm. per second and records were taken on a transverse sweep triggered at 25 per second from a precision quartz oscillator also yielding coincident time marks on the two beams at 10 millisecond interval.[8]

Action currents were recorded either from the two phrenics or from one phrenic and one vagus nerve, or from the two vagi, first with "eupnoeic" respiration or ventilation, then under "dyspnoea." Dyspnoea was obtained on the spontaneously breathing animal either by closing the tracheal cannula or by replacing the inspired air or oxygen by a mixture of 40 per cent carbon dioxide and 60 per cent oxygen. Dyspnoea, with the chest opened, was produced either by sudden stop of artificial respiration at collapse position of the lungs or by reducing ventilation to a low level steady state attained with a five- to ten-minute time lag, as controlled on the electrophrenicogram.

RESULTS

In all 10 experiments (see Table I), in which the action currents of the two phrenic nerves were compared, synchronization was found to be perfectly "in phase" between the two sides. This is illustrated in the three examples of Figure 1. In spite of some difference in shape between the corresponding synchronized volleys, the latter coincide with their maximum

TABLE I. SYNOPSIS OF EXPERIMENTS

Exp. no.	Body weight	Urethane g	Thorax closed	Thorax opened	Dyspnoea produced by closing trachea	Dyspnoea produced by lung collapse	Dyspnoea produced by breathing CO_2 + O_2	Records taken from Phrenic r	Phrenic l	Vagus r	Vagus l	Frequency of synchronization Volleys per second (Average ± S.E.)
1	2,5	1,9	+		+					+	+	90
2	2,5	1,9	+		+					+	+	100
3	3,0	3,0	+		+			+	+			115
4	2,2	2,2	+		+			+	+		+	95-100
5	3,2	3,2	+		+			+	+	+	+	110
6	3,3	3,3	+		+			+		+		100
7	3,2	3,2	+		+			+	+		+	no synchron.
8	2,6	2,6	+		+			+	+	+	+	90-100
9	2,2	2,2	+		+			+	+	+	+	105
10	2,7	2,7	+		+			+	+	+	+	95-100
11	3,5	3,5	+		+					+	+	95-115
13	3,0	3,0		+		+				+	+	90-95
14	2,6	2,6		+		+		+			+	95-100
15	3,3	3,3		+		+				+		110
16	3,4	3,4		+		+			+	+		105
17	2,5	2,5		+		+				+		85-90

Exp. no.	*Body weight*	*Urethane g*	*Thorax* closed	*Thorax* opened	*Dyspnoea produced by* closing trachea	closing lung collapse	breathing CO_2 + O_2	*Records taken from* Phrenic r	Phrenic l	Vagus r	Vagus l	*Frequency of synchronization* Volleys per second (Average ± S.D.)
22	3.2	3.2	+		+			+		+		
				+		+			+	+		70
									+	+		
23	3.0	3.0	+		+				+	+		
									+		+	80-100
								+	+		+	
24	2.8	2.8		+		+		+			+	
										+	+	70
25	2.7	2.7		+		+		+		+		
								+			+	85-95
								+	+			
26	3.2	3.2	+				+	+			+	
				+		+		+		+		100
27	2.6	2.6	+				+	+			+	
								+		+	+	90-100
								+		+		
28	3.0	3.0	+				+		+	+		
								+			+	110-120
								+		+	+	
29	2.9	4.4	+				+	+			+	
								+		+		95-105
								+	+			
30	2.5	2.5	+				+	+			+	
										+		100-105
31	2.6	2.6	+				+	+		+		
								+		+	+	80-90
								+	+		+	
32	3.4	3.4	+				+	+			+	
									+	+		100-105
										+	+	
33	2.6	2.6	+				+	+		+		
								+			+	105
									+		+	

amplitude, and no phase shift could be detected over the whole period of synchronized activity.

In the 28 experiments (see Table 1), one phrenic nerve was compared with the ipsilateral (18 cases), with the contralateral (28 cases), or with both (14 cases) vagus nerves. Only in 10 out of 46 instances, i.e., in 7 out of 28 experiments was a more or less pronounced synchronization encountered in the efferent vagus nerve, whereas in the remaining 36 cases (21 experiments) no apparent synchronized activity could be detected in the vagus, although synchronization was very marked in the phrenic (Fig. 2). But in all experiments in which synchronized inspiratory activity was found to develop in the efferent vagus nerve, the vagal response appeared to be as perfectly "in phase" with that of the phrenic as synchronization is "in phase" between the two phrenics. Three examples are represented in Figure 3. Even a few synchronized volleys, when appearing within the vagal efferents, tally with corresponding volleys of the phrenic (Fig. 3 Ar, Al). The rarer event (5 out of 46 vagi in 4 out of 28 experiments) of a marked synchronization of vagal inspiratory activity is shown in Figure 3 B, C, together with the corresponding synchronization in the phrenic.

Direct comparison of the synchronized activity of the two efferent vagus nerves was only possible in 3 out of 10 cases (see Table 1), as illustrated in Figure 4 B, C, D. As a rule, synchronization was present or stronger in one vagus and absent, or much less conspicuous, in the other. But whenever synchronized volleys appeared on both sides, they corresponded with regard to frequency and phase.

In the phrenic as well as in the efferent vagus, synchronization was found to develop most easily during the first half of the inspiration period. Immediate onset of dyspnoea appeared to be essential for producing high-grade synchronization. It was obtained best either by sudden collapse of the lungs and stopping of artificial respiration on the animal with the chest opened, or by admitting high (20 to 40%) concentration of carbon dioxide in oxygen to the spontaneously breathing animal. Synchronization then attained its highest degree during the first five to ten breaths but subsided slowly with continuation of the dyspnoeic state, without, however, disappearing completely. Maximum synchronization, therefore, could not be obtained with slowly developing dyspnoea, i.e., with rebreathing, or with breathing low (4 to 6) per cent carbon dioxide. Rapid and complete recovery from synchronization was achieved by hyperventilation, and this was always necessary as a preliminary procedure in order to induce optimum synchronization again and again.

The frequency values for inspiratory synchronization as observed in these experiments are represented in Table 1. The lower figures mostly refer to

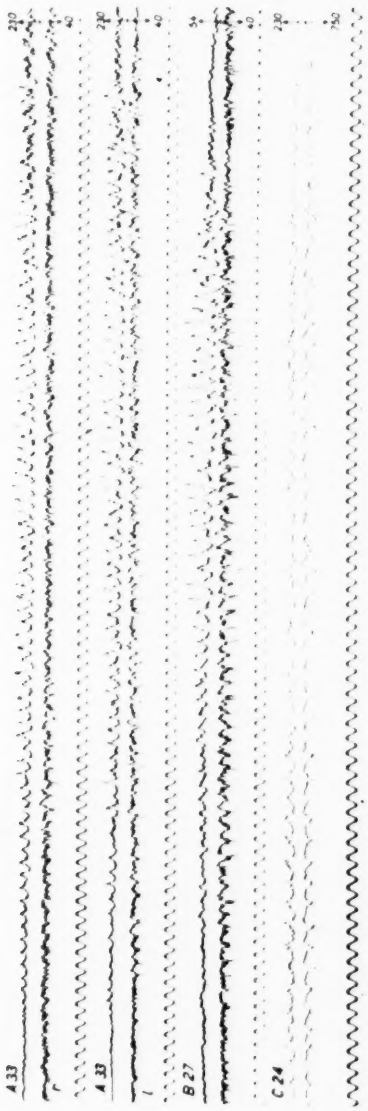

FIG. 3. Comparison of synchronized activity between phrenic nerve (above in A, B; below in C) and vagus nerve (below in A, B; above in C) during early stage of severe dyspnoea. Inspiration period from three different experiments, as numbered on the left. For particulars, see Table I. Time marker: 100 per second, from left to right. Ordinate calibration in microvolts, arrows indicate negativity of proximal electrode.

records taken towards the end of the experiment and were probably due to lowering of body temperature during the later stages of anesthesia.

COMMENT

In the vagal inspiratory efferents, motor synchronization does not occur so frequently as was to be expected from earlier investigations.[1,2] This becomes particularly evident when the results of the present investigation are compared with electrical recordings of the inspiratory activity of nucleus ambiguus,[3] where the percentage of synchronized activity was found to be at least twice as high. Since both groups of experiments were carried out on the same animal species (rabbit) and under same anesthesia (urethane), the only plausible explanation for the inordinately high percentage of synchronized activity found in the experiments with central recording is that with a central electrode a respiratory rhythm is more easily detected when synchronization is present than when it is absent. In this respect, the central recording experiments must be regarded as preselected, and therefore it may be concluded that the vagal inspiratory motoneurons of the rabbit do not participate more frequently in motor synchronization than has been estimated in the present investigations (15 per cent).

Because of the fact, firmly established by the results reported here, that whenever synchronization takes place, the synchronized volleys appear simultaneously from widely separate inspiratory motoneurons, a common pace-making mechanism must be admitted. A direct interaction between motoneurons of different nuclei should not be taken into account, neither for the phrenic motoneurons of the two sides, nor for the phrenic and vagal inspiratory, ambiguus motoneurons, nor for those of the ambiguus nuclei of the two sides. The assumption of a common interneuronic centre, located at a higher, bulbar or suprabulbar level, would certainly provide a more adequate working hypothesis. Whether such a "synchronizing" centre constitutes an essential part of the bulbo-pontine respiratory centre, or whether synchronization depends more directly on higher control, requires further investigation.

SUMMARY

Rabbits anesthetized with urethane were subjected to sudden dyspnoea in order to study synchronization of inspiratory action currents in phrenic and efferent vagus nerves.

In the phrenic, synchronization was obtained in all but one of the 28 experiments, whereas in the efferent vagus it was more or less developed in 7 out of the 28 experiments.

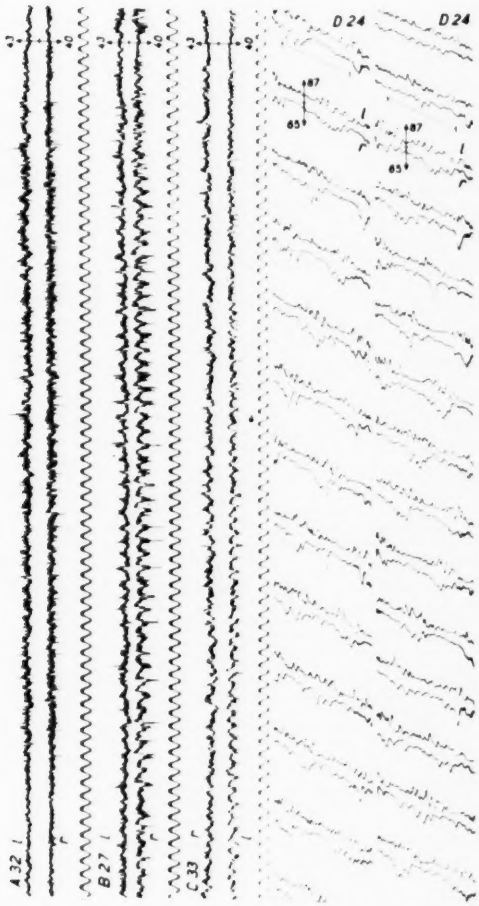

FIG. 4. Comparison of inspiratory activity between the two vagus nerves (r, l) during early stage of dyspnoea. Inspiration period from four different experiments, as numbered on left and top. Note asynchronous activity in A and "in phase" synchronization in B, C, and D. For particulars, see Table I. Time marker on continuous tracings: 100 per second. Time on transverse sweep: 20 millisecond. Ordinate calibration in microvolts; arrows indicate negativity of proximal electrode.

Whenever synchronization was observed it appeared to be perfectly "in phase," i.e., the synchronized volleys occurred simultaneously, not only in the phrenics of the two sides, but also when synchronized activity was compared between one phrenic and one efferent vagus nerve, as well as between the two vagi.

The conclusion is drawn that synchronization of inspiratory motoneurons must depend on a common central mechanism of bulbar or suprabulbar origin.

Conditions for obtaining optimum synchronization are briefly discussed.

REFERENCES

1. Achard, O. and Bucher, V. M.: Courants d'action bulbaires a rythme respiratoire. Helv. physiol. pharmacol. Acta, 1954, *12*, 265–283.
2. Adrian, E. D. and Bronk, D. W.: The discharge of impulses in motor nerve fibres. Part I. Impulses in single fibres of the phrenic nerve. J. Physiol. Lond., 1928, *66*, 81–101.
3. Dittler, R.: Ueber die Aktionsstrome des Nervus phrenicus bei naturlicher Innervation. Pflugers Arch. ges. Physiol., 1910, *131*, 581–588.
4. Dittler, R.: Weitere Untersuchungen uber die Aktionsstrome des Nervus phrenicus bei naturlicher Innervation. Pflugers Arch. ges. Physiol., 1910, *136*, 533–544.
5. Dittler, R. and Garten, S.: Die zeitliche Folge der Aktionsstrome in Phrenicus und Zwerchfell bei der naturlichen Innervation. Z. Biol., 1912, *58*, 420–450.
6. Gasser, H. S.: The analysis of individual waves in the phrenic electroneurogram. Amer. J. Physiol., 1928, *85*, 569–576.
7. Gasser, H. S. and Newcomer, H. S.: Physiological action currents in the phrenic nerve. An application of the thermionic vacuum tube to nerve physiology. Amer. J. Physiol., 1921, *57*, 1–26.
8. Rijlant, P.: L'etude des activites des centres nerveux par l'exploration oscillographique de leurs voies efferentes. I. Centre phrenique et centres moteurs non autonomes du pneumogastrique. Arch. internat. Physiol., 1937, *44*, 351–380.
9. Wyss, O. A. M.: Impulssynchronisierung im Atmungszentrum. Pflugers Arch. ges. Physiol., 1939, *241*, 524–538.
10. Wyss, O. A. M.: Impulssynchronisierung in motorischen Zentren. III. Congr. Neurol. internat., Copenhagen, 1939, 495–496.
11. Wyss, O. A. M.: Die tonische Innervation des Zwerchfells. Pflugers Arch. ges. Physiol., 1941, *244*, 712–735.
12. Wyss, O. A. M.: Eine neue Atmungspumpe fur die kunstliche Atmung im Tierversuch. Verh. Schweiz. Physiol., Jan. 1940, 8–10.
13. Wyss, O. A. M.: Nouveaux appareils électro-physiologiques (IV). Helv. physiol. pharmacol. Acta, 1952, *10*, C 42.
14. Wyss, O. A. M.: Nouveaux appareils électro-physiologiques (V). Helv. physiol. pharmacol. Acta, 1954, *12*, C 9–C 10.

EVENTS

YALE MEDICAL SOCIETY

November 14, 1955

CHELATION IN CONTRAST RADIOGRAPHY. By Robert Shapiro.

The chemistry of chelation was briefly reviewed. The chemistry, pharmacology, and toxicity of lead disodium versenate in various experimental animals were discussed. This material when injected intravenously is predominantly excreted by the kidneys. Thus, between 70-90 per cent of the chelate can be recovered in the urine during the first 24 hours following intravenous injection. As a result of this procedure, an excellent nephrogram-pyelogram is frequently obtained on the 15-minute film. The lead chelate also provides excellent contrast visualization of the cardiovascular system and spleen. Oral administration of this material results in good visualization of the gastrointestinal tract.

Unfortunately, although little or no free lead ions are demonstrable *in vitro*, the material is toxic *in vivo*. The possible mechanisms behind this paradox were discussed.

ROBERT SHAPIRO

ENDEMIOLOGY OF ENTERIC VIRUS INFECTIONS. By Joseph L. Melnick, Edward L. Honig, and Peter Isacson.

An endemiological study of enteric viruses was conducted among 136 normal children living in households in two socioeconomic groups, over a 29 month period in Charleston, West Virginia.

A repeatable seasonal incidence of enteric virus excretion was noted with over 90% of isolations occurring in the months of June to October. Of 592 stools examined in District I, a lower socioeconomic group, 8.3% yielded virus as compared to 3.1% of 966 stools examined in District IV, an upper middle class district with good environmental sanitation. Among the 77 viruses isolated in tissue cultures of monkey kidneys, 44% were orphan viruses, 37% Coxsackie viruses, and 19% poliomyelitis viruses.

Among polio virus carriers and 15 family contacts, 10 individuals had simultaneous heterotypic and type specific antibody responses. The heterotypic ones were usually present at low levels and were transient in nature.

JOSEPH L. MELNICK ET AL.

THE FATE OF PLASMA LIPIDS IN VASCULAR AND AVASCULAR CONNECTIVE TISSUE. By Levin L. Waters.

It has long been suspected that the morphological sequences of early arteriosclerosis follow the entrance of blood plasma into altered intimal connective tissue. To date, post mortem studies and animal experiments have not clarified the possible relationships of local pathogenetic factors and of pathogenetic factors in the ambient blood. The present experiments deal with this subject.

Following selective injury of the coronary arteries of dogs by allylamine, intravenous injection of lipid solutions of human plasma lipoproteins resulted in the deposition of large quantities of sudanophilic material at the sites of arterial injury. The intimal components of the lesions were transformed into foam cellular granulomas within two weeks.

Alimentary hyperlipemia was produced in another series of dogs by meat and egg feeding. While the blood of these animals was lactescent, their coronary arteries were acutely injured by short, maximal hypertensive episodes induced by intravenous epinephrine. Large quantities of sudanophilic material were deposited promptly at the sites of arterial injury. The lipoid, derived from chylomicrons, was not phagocytized and gradually disappeared from the lesions without foam cell accumulation.

These observations prompted a broader investigation of the fate of human plasma lipoproteins and of human and dog chylomicrons in connective tissue. Lipoproteins disappeared rapidly from the subcutaneous tissues of dogs or from the media of dogs' aortas. Human or dog chylomicrons placed in subcutaneous tissue disappeared more slowly, but did not result in the formation of foam cell granulomas. In dog aorta chylomicrons elicited a foam cellular response in some instances.

By placing lipoproteins, chylomicrons, and pertinent control materials in the corneas of anesthetized dogs, observations could be made on the fate of these substances in a collagen rich, avascular connective tissue, more nearly approximating the human aortic intima. Viosterol in vegetable oil remained as oily droplets in the cornea and elicited no inflammatory reaction. Dog or human chylomicrons gave rise to a lipoid rich, foam cellular reaction with little or no other inflammatory response except collagen alteration. While clear normal dog plasma or serum injected into the cornea gave rise to no lipoid deposits, corneas studied one to two weeks after the injection of clear normal human plasma or serum revealed appreciable quantities of sudanophilic material in the stroma. Droplet formation or foam cell accumulation was not observed. However, if denatured (by concentration of serum) human lipoprotein was introduced into dogs' corneas, a lipid rich foam cell reaction was promptly elicited.

In summary, these experiments indicate that lipoids derived from plasma lipoproteins or chylomicrons accumulate in areas of acute arterial injury. Both lipoproteins and chylomicrons, under certain conditions and in certain connective tissue sites, can give rise to morphological sequences that reproduce many of the histological features of early arteriosclerosis.

LEVEN WATERS

PATHOGENESIS OF FEVER. By Elisha Atkins.

Despite extensive work on the physiology of temperature regulation, the sequence of events leading to the elevation of body temperature in both clinical and experimental fevers has remained obscure. It has long been thought that some product of tissue injury, liberated at sites of inflammation, may act upon the thermoregulatory centers of the brain to cause fever.

The demonstration by Bennett and Beeson of a pyrogenic substance extractable from leukocytes has added support to this hypothesis. However, no endogenous pyrogen has hitherto been detected in the circulation. The demonstration of such a substance in the blood of rabbits made febrile by the injection of typhoid vaccine forms the basis of the present study.

By means of a method of passive transfer, the serum of donors sensitized by one or two prior injections but non-tolerant to typhoid vaccine was found to contain a rapidly acting pyrogen similar to that obtained by other investigators from leukocytes and their extracts. This substance appeared after clearance of the originally injected vaccine, and its pyrogenic activity was unaffected by the fever depressing mechanisms involved in tolerance. In contrast, the pyrogenic effect of the uncleared vaccine present in serum obtained shortly after injection was markedly inhibited.

These results indicate that a second pyrogen of endogenous origin, apparently arising from damage of host cells, eventually appears in the blood after inoculation of exogenous bacterial pyrogen. The rapid onset of fever following injection of the endogenous factor suggests that it may well be the essential factor which acts upon the hypothalamus to cause fever.

Preliminary studies with streptococcus and influenza virus suggest that such a substance can also be obtained in other forms of experimental fevers in which bacterial pyrogens do not play a part.

ELISHA ATKINS

ZOOLOGICAL JOURNAL CLUB

November 16, 1955

AN ECOLOGICAL APPROACH TO SOCIAL BEHAVIOR IN MAMMALS. By John King, Jackson Memorial Laboratory, Bar Harbor, Maine.

Generally, laboratory experiments in ecology have been neglected. This is proper, to a degree, since such experiments indicate only what can happen, with confirmation of the reality of the occurrence depending upon fieldwork. Yet this does not render laboratory experimentation valueless. The following are examples of the kinds of problems susceptible to laboratory analysis. While not fully meaningful in and of themselves, they suggest interactions which may be significant in wild populations.

1. *Inter- and intra specific competition* is a problem conceived of as competition for a niche. Food, however, is not necessarily the limiting factor—direct aggression may play a role, too. Comparisons of the aggressive behavior of lab populations of *Mus* and *Peromyscus* indicate that the former is far more ferocious. Thus, it is suggested that under natural conditions *Peromyscus* would be replaced by *Mus* via defeat in outright combat.
2. *Sex and aggression*. The fact that subordinate males may mate while more aggressive males are engaged in combat has been suggested as an explanation for the non-evolution of highly aggressive males in polygynous societies. This possibility can be experimentally tested.

3. *Aggression and development*: Young male house mice (*Mus. m.*) generally do not fight until reaching 34 days of age, while females seldom fight. Injection of testosterone, however, can induce fighting much earlier in males, though equivalent amounts have no effect on the aggressive behavior of females. The same results obtain with gonadectomized mice. This would suggest the existence of a particular neural mechanism, present prior to its activation by hormonal stimuli, and absent in females.

4. *Early experience*: Groups of mice which had been isolated for different periods of time in their infancy showed marked differences in the degree of aggression manifested later in their lives, indicating the importance of early experience on social behavior and organization.

5. *Social factors in viability*: It can be shown that individual growth rates of mice reared in groups of different age-composition and size show significant differences, with minimum viability occurring among the isolates. A number of factors can be important as the proximate mortality factor, though the social factor is an ultimate cause.

6. *Society and environment*: Territoriality involves the maintenance of group integrity as well as a distribution in space. Experiments with breeds of dogs suggest that group territoriality and tolerance of strangers is related to the rigidity of the social organization.

Mammals are keenly aware of their social environment and their basic activities (e.g., food-seeking) are closely related to their social activities. Thus, there is a basic legitimacy in the ecological approach to social behavior.

PETER H. KLOPFER

MICROBIOLOGY SEMINAR

November 18, 1955

COMPARATIVE BIOCHEMISTRY OF PHOTOSYNTHETIC CO_2-FIXATION. By R. Clinton Fuller, Brookhaven National Laboratory, Upton, New York.

In photosynthesis, exposure to CO_2 initiates the formation of phosphoglyceric acid as a major product. It has been postulated that the mechanism concerns two and three carbon intermediates. However, the substrate may be a five-carbon compound such as ribulose-diphosphate with a cyclic system regenerating the substrate. For example, ribulose-diphosphate in the presence of CO_2 yields phosphoglyceric acid which eventually breaks down to triose-phosphate. By rearrangement the sugar can reconstitute the ribulose diphosphate. In fact, it was shown that in the presence of light and water with the proper enzymes ribulose-diphosphate is increased with the commensurate diminution of CO_2 and phosphoglyceric acid.

The question of whether or no such enzyme systems were more widely present initiated studies using cell-free extracts of Chlorella which were incubated with labeled C^*O_2 and ribulose-diphosphate. Large amounts of

phosphoglyceric acid were formed. This was not the case when certain substrate substitutions were tested which included trials with ribulose 5-phosphate, ribulose 3-phosphate, and fructose diphosphate. The actual mechanism is unknown, but the enzymes are not limited to the photosynthetic organisms being present in the naturally occurring, non-photosynthetic counterpart of euglena as well as in the green and blue-green algae and the photosynthetic bacteria. Nevertheless, the enzymes concerned can be shown to be located in the chloroplasts as demonstrated in chloroplasts separated according to special techniques. The reaction is considered significant for the elaboration of mechanisms involved in pentose metabolism.

M. L. I.

ANATOMY SEMINAR

November 22, 1955

The Genetically Obese Mouse. By Dr. John Fuller, Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine.

The preliminary study dealt with the caloric intake responses of the genetically obese mouse and siblings when maintained on three variations of the usual laboratory diet. The variations used were: (1) Caloric dilution — pellets with cellulose; (2) decreased palatability with no caloric change — pellets with quinine; (3) increased palatability and increased caloric values — pellets soaked in fat. On the first day following diet alteration the normal mouse allows its intake to be governed by the superficial characteristics of the diet, e.g. palatability, bulk, with a resultant increase or decrease of calories ingested. After three days its intake stabilizes at that point which equals the pretest caloric intake. The genetically obese mouse will respond to these diet characteristics in the same manner, direction, and to about the same extent as his non-obese sibling. But, while making some correction for the imposed diet change, it is unable to adjust the food intake to pretest caloric levels. An as yet unknown mechanism is suggested which controls intake according to caloric need. This is presumably present in the obese mouse but sluggish in action.

P. R., JR.

PSYCHIATRY RESEARCH SEMINAR

December 8, 1955

A Study of the Preliminary Stages of the Construction of Dreams and Images. By Charles Fisher, Department of Psychiatry, Mt. Sinai Hospital, New York.

If a lantern slide is projected onto a screen for a small fraction of a second (0.01), a subject observing the screen will see a flash of light and nothing more. If the period of exposure is short enough (0.002), not even the flash of light will be perceived. A few words, a number, or a simple pattern, such as a star, projected in this manner will appear in the subject's

subsequent images and dreams in fragmented, distorted, and disguised fashion. These projections which are not perceived by the subject, nevertheless are registered in preconscious levels and then worked into material emotionally significant for the subject and thus appear in the manifest content of dreams and images. It is postulated that such peripheral perception is not actually perceived and then repressed to preconscious and subconscious levels, but rather that it is registered in preconscious levels and never reaches conscious perception, because the stimulus is not of sufficient magnitude to bring it to consciousness. The object thus registered is never reproduced in toto by the subject; only portions are distorted, disguised, and woven into his images and dreams. It is further postulated that dream work actually begins when emotionally charged material is combining with preconsciously registered forms at the time of dreaming, and that these forms are reworked into the material at different times as the dreams or images are constructed.

L. B.

BIOPHYSICS SEMINAR

December 9, 1955

CYTOLOGICAL ASPECTS OF PROTEIN SYNTHESIS. By A. W. Pollister, Columbia University, New York.

The "new cytology" of the last twenty years or so has used many modern techniques (e.g. electron microscopy, cytochemistry, differential centrifugation of cell dispersions) to advance greatly our understanding of the functions of cellular constituents. The following is a brief review of present knowledge of protein synthesis as developed by these methods when applied to such active protein synthesizing tissues as the liver and pancreas of the rat.

The zymogen granules produced by the acinar cells of the pancreas appear to be composites of all the pancreatic enzymes. Their initiation at the bases of these cells, enlargement as they proceed distally, and final release through very temporary breaks in the cell membrane have been observed *in vivo*. Electron microscope studies of the area of initiation (and other portions of the cellular "hyaloplasm") show it to be very highly structured, containing, among other inclusions, a complex of 40-70 Å thick membranes bearing on one surface series of granules averaging 140 Å in diameter. Such structures have been found in all protein synthesizing cells studied so far.

The cytochemically defined distribution of ribose nucleic acid in cells also parallels protein synthesis very closely. Differential centrifugation studies have shown virtually all of this RNA to be in the granules isolatable from the microsome fraction (fragments of the membranes mentioned above). Biochemical studies have shown these granules to be the cellular fraction carrying out the greatest amount of protein synthesis when supplied with appropriate amino acid substrates and an energy source (ATP). The rôle of the RNA in this is still uncertain. The cytochemical distribution of phospho-

lipids in protein-synthesizing cells parallels that of RSA—whether or not this is true in the granule fraction of centrifugates is unknown. Just which compounds are important in protein synthesis is still very much of an open question.

Rough calculations of rates of protein synthesis by liver cell granule fractions, using C 14 labelled amino acids, indicate this fraction alone is capable of accounting for previously measured rates of synthesis for the entire organ (to 9% of dry weight of organ per day as plasma proteins).

The rôle of the nucleus in these processes is very poorly defined. The "pores" in the nuclear membrane demonstrated by electron microscopy, transfers of substances from nucleus to cytoplasm demonstrated by radioautography (in amoebae), experiments with enucleation, and much other evidence indicate the nucleus is not without function in these processes. Perhaps it exerts some sort of indirect control. The function of the nucleolus is also unknown.

MALCOLM S. GORDON

PRESENT-DAY PSYCHOLOGY. A. A. Roback, Editor, with the collaboration of forty experts in the various fields. New York, Philosophical Library, 1955. xiv, 995 pp. $12.00.

In this volume an attempt is made to survey the entire field of contemporary psychology, including not only the traditional topics of academic psychological interest, such as perception, cognition, attention, emotion, etc., but also ranging as far afield as general neurology, psychodrama, speech, hypnotherapy, psychoanalysis, parapsychology, military psychology, and the psychology of literature, art, and religion. In all, forty different subjects are covered, and the book succeeds in pointing out the intensity and diversity of psychological investigation. Some of the topics have rarely been covered in such a survey; and there is at least one on "Contemporary Histories of Psychology" which has not appeared in any other collection.

This reviewer was very much taken with Dr. Roback's brief preface and introduction in which he alludes to the difficulties of an editor and touches on his disappointments with unusual honesty. He mentions that "an interesting booklet could be written on the individual differences of contributors." It probably should be written, since in this age of anthologies, surveys, and symposia it would open for debate not only the relative merit of such publications, but would also bring into focus such problems as the selection of contributors, the range of individual articles, and the rôle of the editor.

There is little uniformity in this volume. Some of the collaborators attempt to cover the entire field in an historical fashion, others emphasize primarily recent contributions. Some of the papers are critical reviews, while others highlight the personal orientation of the writer. Personal bias is difficult to control and it might have been more profitable for the reader if the most controversial topics had been discussed by representatives of different schools of thought. This, of course, would have meant more articles and probably a second volume. And it does seem almost impossible to do justice to the scope of Dr. Roback's approach in one volume. It might perhaps have succeeded if his "ideal" an emphasis on the more recent research had been heeded by his collaborators.

With a few exceptions, the chapters are much too brief; however, they have good bibliographies. If one sees this book as an aerial survey of the field, at times distorted by a differing force of individual surveyors, cloud formation above the subject covered, and angle of approach toward the topic, one can profitably explore where one wants to go for further and more detailed study. This book points up the fact that the pedestrian no longer has a chance to explore the ever growing world of psychology unaided. He now needs lodestars to various points of interest from which he can correlate old and new knowledge.

JAY KATZ

PREMATURE INFANTS. A MANUAL FOR PHYSICIANS. 2d. ed. By Ethel C. Dunham. New York, Paul B. Hoeber, Inc., 1955. xii, 459 pp. $8.00.

Prematurity represents the major cause of neonatal death, the death rate for premature infants being 22 times that for full-term infants. While in-

vestigation continues into the causes and prevention of prematurity, the care of prematures requires constant reappraisal. The second edition of Ethel Dunham's manual on premature infants is both an excellent reference source and guide for the care of these patients.

The first section of the book is concerned with such general considerations as the incidence, causes, and prevention of prematurity and with the prognosis and developmental progress of infants who are prematurely born; the second section deals with clinical problems such as the care and feeding of prematures and the disease states to which they may be subject; the concluding part of the manual deals adequately with the important public health aspects of prematurity. Helpful ancillary data have been included in the appendix.

This monograph is a solid piece of work and may be highly recommended. Rather than having the superficial, sketchy, and dogmatic character of many handbooks, the material presented here is concise, well chosen, and carefully documented. The inclusion of extensive and pertinent bibliography will facilitate further reading.

MORRIS GREEN

THE QUANTITATIVE ANALYSIS OF DRUGS. By D. C. Garratt. New York, Philosophical Library, Inc., 1955. xv, 670 pp. $17.50.

This is the second edition of a book published before the last war under the title, *Drugs and Galenicals*. The intention of the author to keep pace with the considerable expansion of the field of medicinal chemicals has been well met. It is indeed a comprehensive survey of drugs including galenicals, synthetic drugs, metallic elements, and essential oils, as well as complex mixtures of drugs. These substances are listed conveniently in alphabetical order, with separate categories for essential oils and for oils, fats, and waxes. The convenience of this system breaks down, however, when one finds aureomycin, dihydrostreptomycin, and neomycin listed under penicillin, rather than all being listed logically under the general heading of antibiotics.

Two factors seem to have entered into the selection of the textual material. The author admits to leaning heavily upon the accepted methodology of the U. S. and British Pharmacopoeia, although he makes clear that the book is intended to supplement the official compendia by emphasizing quantitative aspects of analysis. Certainly the author's own analytical experience as Chief Analyst of the Boots Pure Drug Company of Great Britain has played no small role in the selection and organization of material and adds to the value of the book.

The format, which includes the indentation of all methods giving experimental details, facilitates rapid consultation and should be appreciated.

A book of this kind must of necessity be intensely practical, yet it is unfortunate when this is carried to the extreme of explaining in a footnote that the "phenol reagent" used in the analysis of epinephrine is "a complicated reagent usually bought ready prepared." Not only is the academic value of the book reduced in this way, but even its practical nature suffers

when one searches in vain for the place where one can buy the reagent. In certain sections, such an approach limits the book's usefulness to the technician's level.

Perhaps the most unfortunate decision the author has made has been to limit the methods described to purely chemical ones. In many instances (e.g., epinephrine), where physical methods (such as spectrophotometry) have been applied with notable success, the fact is not mentioned. This deficiency is weakly compensated for by the inclusion of a brief chapter on general physical methods with few references.

It must be borne in mind, however, that it is probably not possible for a single individual to do complete justice to a review of the book in its entirety. In the general analysis there is no question that this will be a useful handbook for the pharmacologist, toxicologist, pharmacist, and those engaged in allied sciences.

NICHOLAS J. GIARMAN

THE BEHAVIOR OF PULMONARY TUBERCULOSIS LESIONS. By Edgar M. Medlar. New York, Medlar Monograph, 1955. 244 pp.

This monograph presents a summation of Dr. Medlar's studies spanning a quarter of a century. As the author states in his introduction, ". . . it presents the observations and the interpretations of observations of a pathologist who has sought to understand the dynamics of tuberculous disease." The conclusions of a lifetime of research in understanding the time-sequence relationships of ". . . this microscopic, parasitic, vegetable cell . . ." and the human lung are presented for the first time in one beautifully illustrated volume.

The initial chapter includes an excellent summary of the historical landmarks in man's efforts to eradicate the tubercle bacillus. From such a survey Medlar concluded that a true understanding of the dynamics of the disease could not be obtained at the autopsy table. He therefore turned to the laboratory for a 15-year study of tuberculosis in lower animals. By employing rabbits and the bovine tubercle bacillus, he was able to reproduce at will an infection closely akin to that in man. From histological sections the reader may follow the pathological morphology from the earliest focal areas of lobular pneumonia to its ultimate and fatal stages of necrosis and cavitation. The response to varied dosage and the problem of re-infection disease are presented in similar fashion. One wishes that space permitted the author to enlarge on his work dealing with effects of posture. By forcing rabbits to assume an upright position, he was consistently able to produce apical tuberculosis in an animal which ordinarily exhibits only basular lesions. Medlar confesses that an explanation for this phenomenon in the rabbit, as with man, remains a riddle.

Having established the time-sequence relationship in a lower animal, the author then applied this knowledge to a similar study in man. One thousand medical examiner cases with microscopic evidence of tuberculosis and 100 fatal cases of proven tuberculosis were examined with meticulous detail. A missing link was supplied with the advent of resectional therapy, and the

surgeon's blade provided an additional 313 specimens. From this vast quantity of material the author has reconstructed the chronology of the pathogenic process in a dynamic manner. The behavior of the parenchymal lesion, of the bronchial lesion, and of tuberculous bronchiectasis are each discussed separately. The chapter on bacteriological observations should prove valuable to anyone who has searched a slide for the tubercle bacillus.

Although the clinician may be irked by the minutia of pathological detail, it should be noted that succinct case histories accompany each of the specimens. Unfortunately, the corresponding X-rays are at a minimum.

The printing is excellent and the color photomicrographs are superb.

JOHN L. KLINE

MENTAL HYGIENE IN PUBLIC HEALTH. 2d. ed. By Paul V. Lemkau. New York, McGraw-Hill Book Co., Inc., 1955. xii, 485 pp. $8.00.

This second edition of a book which received high praise six years ago, when first published, maintains a high standard in presenting elements of progress and developments in "mental hygiene fields." In order to enable different professionally trained persons in public health and in mental health to work more closely together, new material is brought together on the theoretical basis of mental hygiene work related closely to field problems; and the administration and service responsibilities of government (especially in North America) are outlined, along with newly evolved general principles of programming and extended case illustrations.

"Fortunately," as Dr. Hugh R. Leavell states in the Foreword, ". . . the author points out that 'there are things to do' in the mental hygiene field and tools with which to do them." The author states a basic problem when he observes that "mental hygiene depends primarily on the attitude—changing possibilities of communication between personnel of various degrees of training and the population, the needs of which are to be met."

A dilemma of the mental hygienist is related to two divergent trends in science. With a tendency toward specialization, highly specific techniques are used in an effort to solve highly selected problems. The author cautions that a scientist traveling this road must "put on blinders" so that he will not be distracted by interesting side events and paths that might divert him from his central effort. The second trend involves recognition of the complex problems of the world of reality that must be attacked by all available investigative methods. Related to this trend is the development of astrophysics, physical chemistry, social anthropology, and social psychology for example, including the professional fields dealing with the health and the illness of men. There are practical issues, with controversies and rivalry between disciplines endeavoring to attack the same problem in its different aspects, though with a similar ultimate objective. Examples given are that of defining the rôle of the nurse in relation to that of the social worker, and the contamination of the concept "public health" by the concept "socialized medicine," a confusion that gives rise to many serious problems for both the health administrator and the practising physician, not to mention the medical student.

The volume is divided into two parts: (1) the place of mental hygiene in public health, including factors of responsibility, leadership, methods, organization, and services; and (2) the development of the individual, including factors of personality development, eugenics, and prenatal to so-called old age periods. There is a useful review of psychopathological states and of visual aids, with both an author and a subject index. There are revealed praiseworthy characteristics of common sense, judgment, patience, and thoroughness, along with the author's breadth of experience and knowledge. This is a useful text for medical, dental, nursing, public health, and law students, as well as those in other phases of social science and in education, including the workers on the "firing line" of organized community effort.

IRA V. HISCOCK

THE HORMONES. Vol. 3. Gregory Pincus and Kenneth V. Thimann, Eds. New York, Academic Press, Inc., 1955. xiii, 1012 pp. $22.00.

This volume contains chapters on such divergent subjects as (1) plant hormones, (2) hormones in invertebrates, (3) neurohormones, (4) parathyroid physiology, (5) the pancreas, (6) anterior pituitary hormones, (7) growth hormone and corticotropin, (8) gonadotropins and lactogen, (9) posterior pituitary, (10) thyroid physiology, (11) the chemistry, (12) metabolism and (13) physiology of the steroid hormones, (14) the adrenal cortex, and (15) clinical endocrinology. Seven of the chapters are by contributors to the two earlier volumes of this series and eight are by new contributors. All of the subjects have been covered in the earlier volumes to a major extent. For the greater part, material published since 1948 or 1950 has been reviewed in volume III, that is during the five or seven years since the earlier volumes were published. The volume contains about 720 pages of exposition, tables, and illustrations, 158 pages of reference citations without titles, and 135 pages of author and subject index.

Some of the chapters are almost annotated bibliographies; one has 13 pages of exposition or tables and seven pages of references. Often papers are referred to without comment other than that a study was undertaken. A number of chapters, however, are very well done and the authors have carefully selected and evaluated the papers contributing to the subject and thereby synthesized a critical and more valuable review. The chapters on the parathyroid, neurohormones, gonadotropins and lactogen, the metabolism of steroids, the pancreas and growth hormone, and corticotropin are especially good in this respect.

The longest chapter on the physiology of the adrenal cortex (134 pages), cites 1263 references. The author of this section states that "perhaps three [papers] every day" have appeared on this subject during the past 5 years. A period up to January 1954 is covered in this well outlined and extensive review. The work undertaken on thyroid physiology since 1949 is reviewed in another long chapter (87 pages; 805 references cited). This chapter also contains several informative tables.

The reviewer has not read every page in the book; some chapters have been read carefully and completely and others only sampled by subtopics

A number of errors have been found, "cervical" for "cranial" (page 101) and "splenic" for "splanchnic" (page 107), as well as a few differences in interpretation of what was stated about some of the papers to which reference was made. The major criticism is that this book is largely an annotated bibliography. Many reviews of this type are being published in journals and books. This volume is not a textbook or really a reference book on the subject of hormones. The coverage is great in all chapters, although the apparent objectives of the different authors seem quite divergent, some contributing essentially a bibliography, others a critical and more interpretative review. With such a broad coverage of subject matter, the volume will probably be of greatest value in institutional libraries.

W. E. GARDNER

RECENT PROGRESS IN HORMONE RESEARCH. THE PROCEEDINGS OF THE 1954 LAURENTIAN HORMONE CONFERENCE. Vol. XI. Gregory Pincus, Ed. New York, Academic Press, Inc., 1955. 518 pp. With numerous tables and illustrations. $10.00.

This is the latest volume in a series familiar to endocrinologists and to workers in related fields. The 14 papers presented at the 1954 conference were grouped under the headings "Pituitary Hormones," "Steroid Chemistry and Biochemistry," "Hormones and Abnormal Growth," "Hormones and Aging in Man," "Mechanism of Hormone Action," and "Hormone-Cardiovascular Interrelations." Authors and editor are to be commended for the inclusion of a generous number of tables, charts, and photographs. A bibliography and the discussion are appended to each paper. The book ends with an author and a short subject index for this volume (XI) and a cumulative subject index for volumes I-X.

A paper undertaking to summarize the status of an area of investigation, particularly a new one, is almost always helpful to the specialist within the general field. Whether the same paper is of value to a reader outside the field depends, *inter alia*, on whether he can understand what is written. It is here that an author's skill in exposition is put to the test. There is little doubt that some of these papers will interest and excite non-endocrinologists; Rawson and Ralf's "The Endocrinology of Neoplastic Disease" is, this reviewer feels, outstanding for its stimulus and for organization, lucidity, and conciseness. The essays generally are useful summaries of recent developments in research. When the essayist includes a measure of interpretation and hypothesis, his paper is even more valuable.

THOMAS R. FORBES

BIOCHEMICAL PREPARATIONS. Vol. 4. W. W. Westerfeld, Editor-in-Chief. New York, John Wiley and Sons, Inc., 1955. viii, 108 pp. $3.75.

This volume, the fourth in the series, deserves the same praise given to its three predecessors. It is written clearly and concisely and contains, in addition to the below listed compounds, a group of compounds of biochemical interest whose synthesis has been described in Organic Syntheses through

volume 34. Another feature which had been extended to this volume is a cumulative index for all four volumes of the series.

The preparations of compounds described in the present volume include: galactose-1-phosphate, homogentisic acid, dipalmitoyl lecithin, lactalbumin, lactoglobulin, carnosine, histidinol dihydrochloride, urocanic acid, N-acetylimidazole, glycolaldehyde, sodium glyoxylate, glucose 1-phosphate, tetraacetyl ribofuranose, argininic acid, methionine sulfoxide and sulfone, ethionine sulfone, linolenic acid and its methyl ester, and D-glutamic acid. Although all these preparations have been previously described in the literature, they are presented here in a sometimes modified form and benefit from the advantage of having been checked in another laboratory.

The two enzyme preparations which have been included are alcohol dehydrogenase and inorganic pyrophosphatase. In the opinion of this reviewer the enzyme preparations, which in general are clearly described, should give information about inhibitors, activators, substrate specificity, and Km values; there should be more than a mere reference to them if these preparations are to be of the same value as the others.

The volume certainly should be of interest to students as an illustration of chemical techniques as applied to biochemistry and to researchers as an addition to a growing compilation of biochemical preparations.

SIDNEY V. REEDER

MOLECULAR EVENTS IN DIFFERENTIATION RELATED TO SPECIFICITY OF CELL TYPE. Roy Waldo Miner, Ed. Annals of the New York Academy of Sciences, Vol. 60, Art. 7, pp. 965-1160. New York, 1955.

This publication comprises 11 papers presented at a conference held in New York in October 1954, together with a record of discussion by participants. Attention is focused on factors on the submicroscopic level related to the basic problem of the appearance of different cell types during development. The fact that only animal studies are reported should be noted but this has little bearing on the true scope of the conference. While the report is a sampling of only American work in this area, it nevertheless succeeds in highlighting the present status of the field.

Recent technical trends are indicated by the emphasis on immunochemical methodology, the use of substrates, analogues, and inhibitors and the experimental combination of various cell types *in vitro*. The reports deal with the application of these and other techniques to an elucidation of synthetic patterns, immunochemical events, and the molecular basis of structural organization in cells and tissues. While some of the work reported does not go beyond spatial and temporal correlation of the data, many of the reports deal with controlled manipulations of events in differentiation. The latter type of investigation holds great promise for this level of investigation.

While the papers are exciting in their synthesis of present knowledge, the printed discussions following some of them are all too brief and lack the vigor and stimulation that one might expect from an active exchange of ideas by such a group.

For all those interested in the genesis of specific cell types this publication will provide an excellent picture of present trends in the study of the molecular basis of differentiation.

A. J. COLTOMBRE

BIOFLAVONOIDS AND THE CAPILLARY. By Gustav J. Martin and Albert Szent-Gyorgyi, *et al.* Annals of the New York Academy of Sciences, Vol. 61, Art. 3, pp. 637-735. New York, 1955.

This is a collection of papers by various authors, resulting from a conference held by the Section of Biology, New York Academy of Sciences, February 11, 1955.

Part I (Laboratory Studies) recounts the biochemistry and some of the physiological activities of the bioflavonoids. These compounds appear to be involved in the increased vesicular fragility of choline and vitamin C deficiencies and in such diverse processes as: the reproductive cycle of certain algae; the biochemical activities of ascorbic acid, hyaluronidase, histamine, and epinephrine; the breeding difficulties of sheep grazed on isoflavone-containing feeds; and the hemorrhagic complications of dicoumarol therapy. A general section on the structure of the capillary wall by Dr. Zweifach is of particular interest.

Part II (Clinical Studies) outlines evidence for the use of vitamin C and hesperidin in rheumatic fever, decidual bleeding during pregnancy, habitual abortion, and acute poliomyelitis. As indicated by Dr. Youmans in his summarizing paragraphs, the clinical data are not entirely convincing except in situations where ascorbic acid deficiency is clearcut. An especially interesting case is presented for the importance of vitamin C deficiency in the development of rheumatic fever following streptococcal infection, relating the anti-hyaluronidase like activity of bioflavonoids and vitamin C to the early swelling of ground substance (mucopolysaccharide) and the Aschoff nodule of rheumatic fever, and to the similar lesions of DOC-NaCl salt intoxication.

The diversity and interrelationships of these collected papers should provide much stimulation for all those interested in normal or abnormal capillary functions.

ALLAN V. N. GOODYER

THE REGULATION OF HUNGER AND APPETITE. Franklin Hollander, Ed. Annals of the New York Academy of Sciences, Vol. 63, Art. 1, pp. 1-144. New York, 1955.

This is a series of papers, the result of a conference held in New York City in November 1954, with Franklin Hollander as conference chairman and editor. The published report on the symposium includes 13 papers: by Stunkard (New York), Quigley (Memphis); Mayer (Boston); Brobeck (Philadelphia); Janowitz and Hollander (New York); Grossman (Denver); Snapper (New York); Hollander, Sober, and Bandes (New York);

Harris (Chicago); Lepkovsky (Berkeley); Light (Tuckahoe); Miller (New Haven) covering physiological, psychological, and clinical aspects of the subject. It is impossible in a review to do justice to all of these papers. Each paper is written by a specialist in his field.

As would be anticipated, the papers cover a wide range of interests. A paper on Food Preferences in Man (Snapper) touches on the weird and fantastic and includes fascinating lore on cravings and aversions gathered by the author in the Far East. The contribution by Mayer on Energy Intake and Body Weight consists of a rather detailed 28-page discussion of the Glucostatic Theory and Lipostatic Hypothesis, with interesting diagrams. The use of amphetamine is discussed in a paper by Harris on Appetite Depressants. Brobeck's discussion of Neural Regulation of Food Intake is a thorough one and reviews what is known about the influence of hypothalamus on food intake.

One of the most readable and intriguing papers in the series is the account by Hollander and his collaborators of observations on their 18-year old patient with esophageal obstruction and jejunostomy. The psychological aspects of this case make instructive reading, but they were only noted as an incidental part of the study. In the accompanying discussion a scheme is presented for a psycho physiological experiment in this field.

Interest in this symposium is related, of course, to concern over America's popular malady overnutrition, and with the query as to why some people add weight while others do not. The symposium does not produce a final answer to this question. Those who planned the symposium, as well as those who took part were aware that the title "Hunger and Appetite" is a rather ill defined phrase and in many ways inadequate. It was apparently hoped that these two words could be redefined or new terms found to replace them. The symposium does not succeed in doing this. Hunger has usually been measured in terms of the amount of food eaten. This may be quite satisfactory if the primary interest is one of weight control. Miller's paper suggests that there are other aspects of hunger to be considered.

Hunger and appetite are commonly regarded as psychic correlatives of the actual mechanisms which control nutrient balance. Grossman's paper on Integration of Current Views summarizes present knowledge of these mechanisms and notes that certain hypothalamic centers are definitely involved, but that among the factors which may have a part in regulating this activity are oropharyngeal stimulation, gastrointestinal distention, blood levels of nutrients (e.g. glucose), and tissue stores of nutrients.

The papers, with two or three exceptions, do not present new experimental results, but they do attempt to summarize the knowledge to date and to set forth the newer conceptions developed in this field. While most of the papers are written from the physiological angle, almost every author calls attention to the importance of emotional control. The paper on Emotion in Hunger and Appetite (Bruch) presents examples to illustrate the importance of this factor.

This symposium, while presenting rather scattered data from a large and difficult to define area of knowledge, is a successful one in that it makes a

strenuous attempt to determine the factors involved and prepares the way for a more intensive assault in the future.

WM. H. ADOLPH

GREAT EXPERIMENTS IN BIOLOGY. Mordecai L. Gabriel and Seymour Fogel, Eds. Englewood Cliffs, N. J., Prentice-Hall, Inc., 1955. xiii, 317 pp. $3.95.

CLASSICS OF BIOLOGY. By August Pi-Suñer. Translated by Charles M. Stern. New York, Philosophical Library, 1955. x, 337 pp. $7.50.

While both these source books are more than adequate, *Great Experiments in Biology* is, by and large, the better of the two. *Great Experiments* contains 63 excerpts or complete papers and *Classics of Biology*, 75. Gabriel and Fogel have made the better selection and have organized their work better than Pi-Suñer, but the latter has written more adequate introductions to his various sections. Both books concentrate on nineteenth and twentieth century biology, having about 85 per cent of their items from this period. Galen, one of the greatest experimental biologists, is not represented in either and, more surprisingly perhaps, neither is Harvey. Several of the works excerpted in Pi-Suñer's books are certainly not "classics"—a criticism which cannot be leveled at Gabriel and Fogel. Any biologist who has more than a technician's interest in biology will find either book enjoyable and useful, but for students, *Great Experiments in Biology* is undoubtedly superior.

FREDERICK G. KILGOUR

NEURO-VASCULAR HILA OF LIMB MUSCLES. By James Couper Brash. Baltimore, The Williams & Wilkins Co., 1955. xvi, 100 pp. $7.00.

Since 1855 a number of studies have been made concerning the points of entry of nerves into limb muscles as a practical utility of knowledge of the motor points of muscles. These studies omitted any reference to the points of entry of the blood vessels. It was the primary object of the well qualified author of this small atlas to study the entrance of the primary blood supply to limb muscles in order to provide accurate data for the diagnosis and treatment of the results of injuries affecting them. This necessarily included the checking and extending of the observations already recorded on the points and mode of entry of the nerves, for the principal arteries are often closely associated with the point of nerve entry to constitute a definite "neuro-vascular hilum."

The data were compiled from dissections of about 70 upper and 70 lower limbs. Each limb muscle is treated individually, and the frequencies in per cent of the various positions of entry of the nerves and arteries are listed. The results of a number of previous observations on nerve entry by other investigators are also listed. The atlas contains full-page, unlabeled line drawings of each muscle and associated bones which are quite clear and accurate. The nerves and arteries are in color. The paper, print, and binding are of good quality.

The title states exactly what the atlas contains. No mention is made of the origin, insertion, or function of the muscles discussed. This greatly limits the number of persons who would find this atlas of any great value. Those who have need of the information it includes should find it a valuable addition to their libraries.

E. S. CRELIN

PROCTOLOGIC ANATOMY. By R. V. Gorsch. Baltimore, William and Wilkins, 1955. xv, 310 pp. $8.00.

This is an excellent anatomic discussion. The photographs of dissections are somewhat difficult to follow, but the excellence of the diagrams in many areas makes up for this. The book is highly recommended for all specialists in the field.

HOWARD M. SPIRO

A METHOD OF BALANCED ANESTHESIA IN GENERAL SURGERY, OBSTETRICS, AND DENTISTRY. By Sylvan M. Shane and Harry Ashman. Baltimore, Lowry and Volz, 1955. 53 pp. $2.25.

This monograph discusses a method of producing surgical anesthesia to which the eponym "Shane-Ashman" or, more briefly, "S-A" has been applied by the authors. This technique is unequivocally recommended by the authors for all patients, there being no contraindications either of age or concurrent disease. Since no statistical information regarding clinical results is presented, clinical impression must form the basis for the statement that no difficulty has been encountered in over 20,000 cases. No physiological studies are mentioned which have been performed either experimentally or on patients which would tend to support, or perhaps abnegate, certain unusual claims made for the technique. Polypharmacy plays a large rôle in this type of anesthesia, on the theory that by multiple administrations of small amounts of many drugs only the salutary effects of each drug are obtained, thereby eliminating all adverse effects. The discussion of the pharmacology of anesthetic agents is characterized by categorical statements, often misleading, that are at variance with established fact. The bibliography is scanty and weighted with "personal communications." There is no index. The book is well printed and carefully edited, but it is recommended to few.

N. M. GREENE

UNDERSTANDING SURGERY. Robert E. Rothenberg, Ed. New York, Pocket Books, Inc., xviii, 620 pp. $.50.

Realizing that in large part the fear with which many patients regard surgery "stems from a lack of knowledge concerning their illness and the operative procedure which is to be performed on them," this little volume attempts logically to dispel that fear. The entire gamut of surgical conditions is briefly covered; general, orthopedic, gynecological, eye, nose, and throat, genito-urinary, and plastic surgery are discussed. Each chapter in-

cludes an elucidation of the common surgical conditions in that area, indications for operation, discussion of prognosis, and an excellent section answering those questions most frequently asked by patients.

While intended primarily for the lay public, this book obviously is of value to anyone dealing with patients. It might also, in a general way and by bringing together loose ends, be of value to the student who has failed to see the forest for the trees.

By utilizing the popular pocket edition medium this book is made available at the price of fifty cents.

J. C. C.

THE FORESEEABLE FUTURE. By George P. Thomson. Cambridge, University Press, 1955. 160 pp. $12.50.

As Sir George Thomson puts it in his preface, this little book "deals chiefly with the future of technology," and "technology is governed by scientific principles, some of which are understood, and there is accordingly a basis for prediction." In addition to chapters on "Energy and Power," "Materials," "Transport and Communications," and "Food," Sir George has written on "Meterology," "Some Applications of Biology," "Some Social Consequences," and "Thought, Artificial and Natural." The book is not science fiction but is an optimistic, sober, and convincing estimate of many of the developments that may be expected to occur in the next hundred years or so.

Sir George, a Nobel Laureate and son of another Nobel Laureate, Sir J. J. Thomson, the discoverer of the electron, is an atomic physicist who has worked on problems in aviation and atomic energy during the two great wars. His practical experiences plus his obviously wide-ranging scientific interest qualify him admirably for predicting the foreseeable future.

Most will agree with the majority of Sir George's predictions, although it would probably be impossible to obtain unanimity as to which majority. The book is thought provoking, interesting, and well written. Anyone who cares to know something about where we are going should read it. It should reduce the element of surprise at some future developments when they actually occur.

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